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THE INTERACTION BETWEEN HORMONAL AND IMMUNE MECHANISMS UNDERLYING THE POTENTIAL ANTAGONISM OF SIMULTANEOUS TRAINING FOR AEROBIC ENDURANCE AND STRENGTH

BY

LORRIE J. HORNE

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A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

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WE DON'T KNOW WHO WE ARE,
UNTIL WE SEE WHAT WE CAN DO ...

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled, "The Interaction Between Hormonal and Immune Mechanisms Underlying the Potential Antagonism of Simultaneous Training for Aerobic Endurance and Strength" submitted by Lorrie J. Horne in partial fulfilment of the requirements for the degree of Master of Science.

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Dr. G.J. Bell

Dr. S. Warren

Date: January 17, 1995

DEDICATION

I dedicate this thesis to my Mom & Dad, **Georgetta and Dennis Horne**. They have been the cornerstones in my life providing me with tremendous support, encouragement, and unconditional love. They are the driving force behind teaching me that hard work, being dedicated, and standing up for myself and my beliefs are at the heart of happiness, self-satisfaction, and success.

Abstract

Forty-four healthy female (n=17) and male (n=27) subjects were randomly assigned to four training groups; strength training only (S) n=10, endurance training only (E) n=11, and combined strength and endurance training (S&E) n=13, and a control group (C) n=10. The strength and endurance only training groups performed training sessions of progressive intensities 3 times per week for 12 weeks. The combined group completed the same strength and endurance training programs as the other two groups concurrently (ie. 6 days a week). Strength, maximal oxygen consumption, venous blood samples, and 24 hour urine samples were collected prior to and after 6 and 12 weeks of training. Blood serum TNF-α, testosterone, and urinary cortisol levels were measured. There were significant gender differences for strength, maximal oxygen consumption, testosterone, urinary cortisol, and TNF-α that varied between groups. Increases in strength and endurance occurred after training in both genders ($p<.05$). However, gains in strength were greatest in the strength only group compared to all other groups ($p<.05$). No changes were observed in testosterone with training. Urinary cortisol was highest in the combined group ($p<.05$) for females and in the endurance and strength groups for males after training. TNF-α was significantly elevated in the endurance group after training for the females. No changes in TNF-α were observed in males. These results suggest that gender differences exist in the response of TNF-α and urinary cortisol to differential training programs.

Index Terms: TNF-α, Testosterone, Urinary Cortisol, Physical Activity

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Table of Contents

Chapter 1 INTRODUCTION

Introduction 1

Purpose 4

Hypothesis 4

Chapter 2

THE INTERACTION BETWEEN HORMONAL AND IMMUNE MECHANISMS UNDERLYING THE POTENTIAL ANTAGONISM OF SIMULTANEOUS TRAINING FOR AEROBIC STRENGTH AND ENDURANCE

Introduction 10

Methods 12

Subject and experimental design 12

Physical training programs 13

Physiological Assessments 14

Laboratory procedures 15

Assay procedures 16

Statistical analysis 17

Results 17

Discussion 35

References 39

Appendix A: Review of Literature 45

List of Tables

Table 2-1 TNF-α (pg/ml) calculated mean values ± SEM for before, 6 weeks, and 12 weeks of training 18

Table 2-2 Testosterone (ng/ml) calculated mean values ± SEM for before, 6 weeks, and 12 weeks of training 23

Table 2-3 Cortisol (ug/ 24 hours) calculated mean values ± SEM for before, 6 weeks, and 12 weeks of training 26

Table 2-4 $\dot{V}O_2$ max (l/min) calculated mean values ± SEM for before, 6 weeks, and 12 weeks of training 29

Table 2-5 One repetition maximum knee extension strength (lbs) mean values ± SEM before, 6 weeks, and 12 weeks of training 32

List of Figures

Figure 2-1 Female TNF-α (pg/ml) mean values ± SEM (excluding one value) before, 6 weeks, and 12 weeks of training 19

Figure 2-2 Male TNF-α (pg/ml) mean values ± SEM before, 6 weeks, and 12 weeks of training 20

Figure 2-3 TNF-α (pg/ml) mean values ± SEM for all female subjects before, 6 weeks, and 12 weeks of training 22

Figure 2-4 Female testosterone (ng/ml) mean values ± SEM before, 6 weeks, and 12 weeks of training 24

Figure 2-5 Male testosterone (ng/ml) mean values ± SEM before, 6 weeks, and 12 weeks of training 25

Figure 2-6 Female urinary cortisol (ug/24 hours) mean values ± SEM before, 6 weeks, and 12 weeks of training 27

Figure 2-7 Male urinary cortisol (ug/24 hours) mean values ± SEM before, 6 weeks, and 12 weeks of training 28

Figure 2-8 Female $\dot{V}O_2$ max (l/min) mean values ± SEM before, 6 weeks, and 12 weeks of training 30

Figure 2-9 Male $\dot{V}O_2$ max (l/min) mean values ± SEM before, 6 weeks, and 12 weeks of training 31

Figure 2-10 Female One repetition maximum knee extension strength (lbs) mean values ± SEM before, 6 weeks, and 12 weeks of training 33

Figure 2-11 Male One repetition maximum knee extension strength (lbs) mean values ± SEM before, 6 weeks, and 12 weeks of training 34

Chapter 1

The Interaction Between Hormonal and Immune Mechanisms Underlying the Potential Antagonism of Simultaneous Training for Aerobic Endurance and Strength

Introduction

Recently, society has witnessed an increased interest in physical training for the purpose of sport and fitness. Individuals from all walks of life have taken an interest in the available modes of training and in diversified training methodologies. As a result of this change in attitude toward physical activity, sport physiologists have investigated not only the effectiveness of such pursuits, but also the related complications.

In recent years, a popular fitness training technique has incorporated the utilization of concurrent strength and endurance training regimes. In the past, this "cross training" methodology was employed primarily by advanced level athletes and coaches. However, concurrent strength and endurance training is now common at all levels of athletic participation. With the increased interest and utilization of this mixed type of training, complications develop as a result of a change in the homeostasis of the body due to an imbalance between the physiological stress applied via the exercise load, physiological adaptation, and recovery following training. The end result may be a plateau or a decreased level of performance. This net change may be attributed to a variety of factors including alterations in the functions of both the immune and endocrine systems.

The objective of training programs are to enhance the physiological efficiency of the tissues involved in the successful performance of sport movement. It is the objective of the athlete to train in order to increase the strength and thus achieve an increased efficiency and threshold of the soft tissue structures involved. The commonly accepted hypothesis is that achieving a higher threshold will

enable the soft tissue to function without failure. Thus, the goal of training programs are to achieve the highest physiological state possible, without inducing micro-trauma or gross trauma that would result in adverse pain, swelling, or inflammation, and thereby reduce performance. Thus, the purpose of training is to maximize performance through the systematic overload of the energy systems, while maintaining the homeostasis of the body and tissues involved (Vailas et al, 1990).

The importance of concurrent strength and endurance training in sport has become an issue of interest in the past decade. An early research study (Hickson, 1980) investigated the interaction between the two distinct modes of training, and combinations thereof and coined the phrase "interference effect" to denote the decreases in strength gains that occur as a result of combining strength training with endurance training with no decrement in aerobic endurance parameters (VO_2 max). Important implications for training methods have resulted from this research and the ramifications of such combined training programs. Other research has identified that significant alterations occur in the homeostasis of the body as a result of concurrent endurance and resistance training, thereby compromising strength gains but not maximal oxygen consumption (Dudley and Djamil, 1985; Albernethy et al., 1993; Hunter et al, 1987; Bell et al, 1991). The later studies have supported the existence of an "interference effect" in strength development. Furthermore, Bell et al. (1991) found that the lack of strength gains with combined strength and endurance training coincided with a lack of change in skeletal muscle cross-sectional area, as demonstrated by computer tomography scanning. The interference effect has not been shown to be universal as other research has shown no compromises in strength with combined strength and endurance training (Sale et al., 1990) or a compromise in aerobic endurance parameters (Nelson et al., 1990). However the majority of research has found a compromised strength gain with combined strength and endurance training programs.

Despite the number of studies that have been conducted, only a few have attempted to elucidate the underlying mechanism as a result of combined strength and endurance training (Bell et al., 1991; Sale et al., 1990; Nelson et al., 1990). The underlying reasons for the lack of muscle hypertrophy after concurrent aerobic endurance and strength training shown in one study (Bell et al., 1991) is unknown. However, research has identified that the endocrine system responds differently to the two modes of training (Jensen et al, 1993; MacConnie et al, 1986; Hakkinen et al, 1988; Hackney et al, 1989). Endurance training produces an increase in urinary cortisol and a decrease in total testosterone in blood serum, suggesting that the muscle is in a catabolic state (Kuppasalmi and Adlercrutz, 1985). Conversely, an almost reverse response occurs with the hormonal response to strength training, in that there is an increase in testosterone and a decrease in cortisol, which would be conducive for protein synthesis (Hakkinen, 1988; Kraemer, 1988; Jensen et al., 1991; Knoppasalmi and Aldercreutz, 1985; Hackney,1989). The hormonal effect of combining two divergent forms of training such as strength and endurance in the same program has not been investigated.

Recent research has also shown that the immune system can be altered by changes induced by exercise (Gilbert, 1991; Gray et al, 1993; Haahr et al., 1990; Mackinnon, 1992; Nash, 1994; Neiman, 1989; Smith and Weidemann, 1990; Tvede et al, 1993; Vailas, 1991). The combination of the aforementioned factors are hypothesized to interact, thereby altering the balance and homeostasis of protein metabolism in skeletal muscle. Supporting research conducted by Kuppasalmi and Adlercrutz (1985) indicates that endocrine effects on body functions are a result of a balance between many different hormones and their receptors in the target tissues. As a result, protein metabolism is regulated and balances between the anabolic and catabolic states. Some of the important hormones that regulate the equilibrium of this process are testosterone and cortisol.

Purpose

The purpose of the investigation was to evaluate the elements known to be characteristic of endurance and resistance training that may be influenced by hormones (testosterone and urinary cortisol) whose response in turn, may interact with cytokines (TNF-α). Specifically, the effect of strength training, endurance training, and combined strength and endurance training was compared with controls on the following dependent measurements: one repetition maximum knee extension strength; maximal oxygen consumption; tumor necrosis factor alpha; serum testosterone; and urinary cortisol.

Hypothesis

The hypothesis was that an antagonism in the adaptations to training for strength and aerobic endurance when performed simultaneously would occur and that an interaction between cytokine production (TNF-α) and hormone levels (cortisol and testosterone) may be an underlying factor. This interaction would include an increase in TNF-α corresponding to an increase in urinary cortisol and decreases or no change in testosterone. Differences due to training may be observed in TNF-α, testosterone, and urinary cortisol levels between the strength, endurance, combined strength and endurance, and control groups, as well as between males and females. Additionally, strength but not aerobic endurance ($\dot{V}O_2$ max) may be compromised in comparison to the strength group, and finally circulating levels of TNF-α and urinary cortisol may be highest in the combined strength and endurance group in comparison to the strength and endurance groups due to differences in the relative volume of training.

Thus, the following research questions were to be answered:

1. Is there an antagonism present in adaptations to concurrent training for strength and aerobic endurance ?

2. If so, is there an interaction between cytokine production (TNF-α) and hormone levels (cortisol and testosterone) which may be an underlying factor ?

3. Will training cause increases in TNF-α corresponding to an increase in urinary cortisol and / or decrease, or no change in serum testosterone ?

4. Additionally, will there be differences between training groups and genders ?

5. When concurrent strength and endurance training is performed, will strength gains but not aerobic endurance ($\dot{V}O_2$ max) be compromised in comparison to gains in the strength group and the endurance group ?

6. Will the combined group elicit the highest circulating levels of TNF-α and urinary cortisol in comparison to the strength and endurance groups due to differences in the relative volume of training ?

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Chapter 2

The Interaction Between Hormonal and Immune Mechanisms Underlying the Potential Antagonism of Simultaneous Training for Aerobic Endurance and Strength

Introduction

The importance of concurrent strength and endurance training in sport has become an issue of interest in the past decade. An early research study (Hickson, 1980) investigated the interaction between the two distinct modes of training, and combinations thereof and coined the phrase "interference effect" to denote the decrease in strength gains that occur as a result of combining strength training with endurance training with no decrement in aerobic endurance parameters. Important implications for training methods have resulted from this research and the ramifications of such combined training programs. Other research has identified that significant alterations occur in the homeostasis of the body as a result of concurrent endurance and resistance training, thereby compromising strength gains but not maximal oxygen consumption (Dudley and Djamil, 1985; Albernethy et al., 1993; Hunter et al, 1987; Bell et al, 1991). The later studies have supported the existence of an "interference effect" in strength development. Furthermore, Bell et al. (1991) found that the lack of strength gains with combined strength and endurance training coincided with a lack of change in skeletal muscle cross-sectional area, as demonstrated by computer tomography scanning. The interference effect has not been shown to be universal as other research has shown no compromises in strength with combined strength and endurance training (Sale et al., 1991) or a compromise in aerobic endurance parameters (Nelson et al., 1991). However the majority of research has found a compromised strength gain with combined strength and endurance training programs.

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The purpose of this study was to investigate the effect of concurrent strength and endurance training on 1 RM knee extension strength adaptations, the response of hormones (testosterone and urinary cortisol), and the response of the immune system (TNF-α) to training using four groups of male and female subjects (strength only; endurance only; combined strength and endurance; and control group). Since all previous studies (Hickson, 1980; Dudley and Djamil, 1985; Hunter et al, 1987; Sale et al., 1990; Bell et al., 1991; Albernethy et al., 1993) investigating physiological adaptations to concurrent strength and endurance training have not shown an antagonism with aerobic endurance adaptations, this was not the specific purpose of the study. Rather, determining the effect of concurrent strength and endurance training on the response of immune (TNF-α) and hormonal (testosterone and urinary cortisol) parameters on strength gains was of interest.

Methods

Subjects and Experimental Design

Forty-four healthy male and female volunteers were separately randomly assigned to three training groups; strength training only (S) n=10; endurance training only (E) n=11; combined strength and endurance training (S&E) n=13; and a control group (C) n=10. Data was collected on twenty-seven male and seventeen female subjects who had not formally trained, but were physically active prior to the study. The experimental design consisted of randomized group, pretest, post-test design (Campbell & Stanley, 1963). All volunteers participating in the study were required to performed 12 consecutive weeks of individualized training. The strength training only group and the endurance training only group trained 3 days/week while the combine strength and endurance training group trained 6 days/week. Training was performed for twelve weeks since previous research has shown antagonism in training adaptations between seven and ten weeks. The mean(± sd) age, height, and weight for all subjects was 22.3 ± 3.3 years, 175.8 ± 9.3 cm, and 73.4 ± 11.6 kg, respectively. This project was approved

by the Faculty of Physical Education and Recreation Ethics Committee for the use of human subjects in research.

Physical Training Programs

Strength

The strength group performed a combination of machine loading systems (Universal) and free weights including four lower body exercises that utilized the major muscle groups involved in cycling (knee flexion, knee extension, leg press, and calf raises) and four upper body exercises (bench press, seated lat pulldowns, upright row, shoulder pulls). The intensity and volume of training was monitored, programmed, and progressively overloaded using a software package (B.E. Software, Lincion, Nebraska) which allows the quantification of resistance training volumes and intensities. Total training volume load increased approximately 4% every 3 weeks (ie. 70 to 79%) and intensity (relative to 1 RM) increased approximately 4% every 3 weeks (ie. from 72 to 84%). Previous research has shown similar strength training regimes are effective (Bell et al., 1993).

Aerobic Endurance Training

The endurance group trained on Monark cycle ergometers (Model 818 Swede) at a prescribed intensity and duration. Continuous training sessions were conducted twice per week and the duration of training sessions began at 30 minutes and progressed to 42 minutes (4 minute increase every 4 weeks). Subjects exercised at power output equivalent to that at ventilation threshold. Interval sessions were performed one time per week at a work to rest ratio of 1:1 (3 minutes:3 minutes per set). Intensity of interval exercise was equivalent to a power output of 90% $\dot{V}O_2$ max starting at four sets and increasing by one set every four weeks until 7 sets were completed. Heart rates were also monitored every session using Polar Pacer heart rate monitors (Polar Elector, Sweden). Bell et al. (1988; 1991a; 1991b; 1993) previous research has shown similar endurance training regimes are effective.

Combined Aerobic Endurance and Strength Training

The combined group performed the same strength and endurance training programs as described above on separate days (6 days per week) for 12 weeks.

Physiological Assessments

Data was collected and physiological assessments performed on all volunteers prior to, after 6 weeks, and after 12 weeks of training with the exception of the control subjects. The control group was assessed prior to the commencement of training and following 12 weeks of training in order to decrease the cost of analysis associated with the physiological and laboratory testing procedures and to decrease the number of aversive measurements (ie. muscle biopsies, and blood samples) made on the control group. Collection of control subject data in this manner was viewed viable since changes in hormonal, cytokine, and physiological parameters were not expected due to subjects inactivity. Data collected at the above times assessed maximal oxygen consumption, 1 repetition maximum strength, venous blood samples, and 24 hour urine samples.

Assessment of maximal oxygen consumption ($\dot{V}O_2$ max) and determination of ventilation threshold was performed using a standardized incremental exercise protocol to volitional exhaustion on a Monark cycle ergometer using open circuit spirometry (Horizon metabolic cart, Sensor Medicus, California). Ventilation threshold was determined as the lowest point on the V_E/V_{CO2} vs power output (W) relationship described by Bhambhani and Singh (1988). Heart rate was determined using a calibrated Polar Pacer heart rate (Sweden) monitor.

Strength was assessed using a voluntary one repetition maximum (1RM) test for right unilateral knee extension. The subjects performed a five minute warm-up on a cycle ergometer followed by a light set of 10 repetition of knee extension on a universal knee extension machine (Universal). A second set of 8

repetitions was performed at a higher load (approximately 70% of 1 RM). The subjects than completed 2 repetitions of increasing loads until only 1 repetition could be performed. This usually took 3-4 sets and was measured to ± 2.5 lbs.

Venous blood samples (8 ml) were collected at rest after 48-72 hours of no training to determine TNF-α and total testosterone. Blood samples were collected between 4 pm and 6 pm in the afternoon. Consistent collection time late in the afternoon ensured that testosterone measurement would reflect a resting basel level (Cumming et al, 1989). This method ensured that detected changes in circulating testosterone levels would be an accurate reflection of adaptations due to training at the resting state.

24 hour urine samples were collected to determine 24 hour urinary cortisol samples. Urine samples were collected in 2 litre polypropylene bottles at home over a 24 hour period after no training for 24-48 hours in order to obtain a sample reflective of a rested state following training.

Laboratory Procedures

All samples were stored frozen (-80°C) to enable the assays to be performed at the same time to reduce inter assay variability. Whole blood samples were spun at 2000 (xg) for 10 minutes in a IEC CENTRA-7R refrigerated centrifuge. Following separation, the serum portion of the sample was stored in a capped polypropylene test tube and frozen at -80°C until thawed for analysis. Following the first thawing of the samples, the remaining sample was aliquotted into 100 ul portions and re-frozen. 24 hour urine samples were measured to determine total volumes and a 10 ml samples of urine were extracted and frozen at -80°C for later analysis.

Assay Procedures

TNF-α was assayed in duplicate using enzyme linked immuno-assay (ELISA) (INCstar). Radioimmunoassay (RIA) methods (Diagnostic Products Corporation) were used to measure cortisol and testosterone, in duplicate respectively. All assay methods conformed to the procedures outlined in the kits. For detailed description, refer to RIA kit numbers TKC01 and TKTT1 for coat-a-count cortisol and coat-a-count testosterone kits respectively and kit number 40175 for the TNF-α ELISA assay. All subject samples (prior to training, 6 weeks, and 12 weeks) were analyzed using the same kit to decrease the variability associated with different assay kits, as well as the technical instruments used (counters, pipets, ect.).

Duplicate samples of TNF-α were analyzed and read using computer assisted interpretation with a UV MAX Kinetic microplate ELISA reader (Molecular Device Corporation, Menlow Park, California) and SOFTMAX software. The microtitar plate was read at 450 nm with a reference filter of 630 nm. A standard curve was constructed to determine the sample concentrations corresponding to the optical density (optical density) read on the microtitar plate. The OD was plotted on the ordinate against the standard concentrations on the abscissa using CURFIT software curve fitting program to determine sample concentration in pg/ml.

Duplicate samples of testosterone and cortisol were analyzed using RIA kits as described above. All samples were counted for 1 minute with a gamma counter. Results were reported in counts per minute (CPM) for both the standard curve and subject sample. CPM were fitted to a standard curve using CURFIT software curve fitting program using a spline function to determine the final concentrations of testosterone (ng/ml) and cortisol (ug/ml). Final cortisol concentration was expressed relative to 24 hour urine volume (ug/24 hour).

Statistical Analysis

Statistical analysis (Statistica Software, Texas) of each dependent variable was performed using a three-way analysis of variance to compare the main effects of gender (2), group (4), and the effect of training (pre and post only). Multiple comparisons to determine differences as a result of significant F ratios were performed using a Newman Keuls post hoc analysis. Additionally, a three-way analysis of variance was performed using 2 gender X 4 group X 3 time (before training and following 6 and 12 weeks of training) for comparison of dependent measures without the control group to determine the time course of adaptations due to training. Alpha was set at $p<0.05$ for all analysis.

Results

Changes in TNF-α are represented in Table 2-1, Figure 2-1, and Figure 2-3. This data excluded one female subject that had an unusually elevated TNF-α level after 12 weeks of training which was unexplainable. Significant main effects were observed between females and males ($F=3.35$, $p<0.05$), but not between groups prior to training indicating higher TNF-α levels in the male strength only and endurance only groups. Following training, a significant interaction was observed between training groups and genders ($F=5.62$, $p<0.05$), with the female endurance group being significantly higher than all other groups in comparison (male or female). Female subjects were significantly higher than males subjects in the endurance group following 6 and 12 weeks of training. Additionally, the female endurance group was significantly higher than the female strength, female combined and the female control group following both 6 weeks and 12 weeks of training. There were no significant differences observed between the male training groups or the control group following 12 weeks of training.

Table 2-1 TNF-α (pg/ml) calculated mean values ± SEM for before, 6 weeks, and 12 weeks of training.

	Before	6 Weeks	12 Weeks
Control Females n=5	0 ± 0		11.17 ± 15.87
Control Males n=5	0 ± 0		0 ± 0
Strength Females n=2	2.77 ± 1.99	6.64 ± 3.98	0.32 ± 0.48
Strength Males n=7	9.48 ± 3.03	10.80 ± 4.57	5.81 ± 2.90
Endurance Females n=4	5.58 ± 3.73	37.84 ± 24.72**	17.59 ± 6.38*
Endurance Males n=7	5.69 ± 4.44	5.98 ± 3.98	5.87 ± 2.71
Combined Females n=5	4.51 ± 1.99	8.05 ± 3.98	4.46 ± .48
Combined Males n=8	2.28 ± 1.92	4.70 ± 0.47	5.56 ± 2.90

Note: The mean TNF-α value including the high female strength value = 68.87 pg/ml

** Significantly different from before training, $p<0.05$

* Significantly different from 6 weeks of training, $p<0.05$

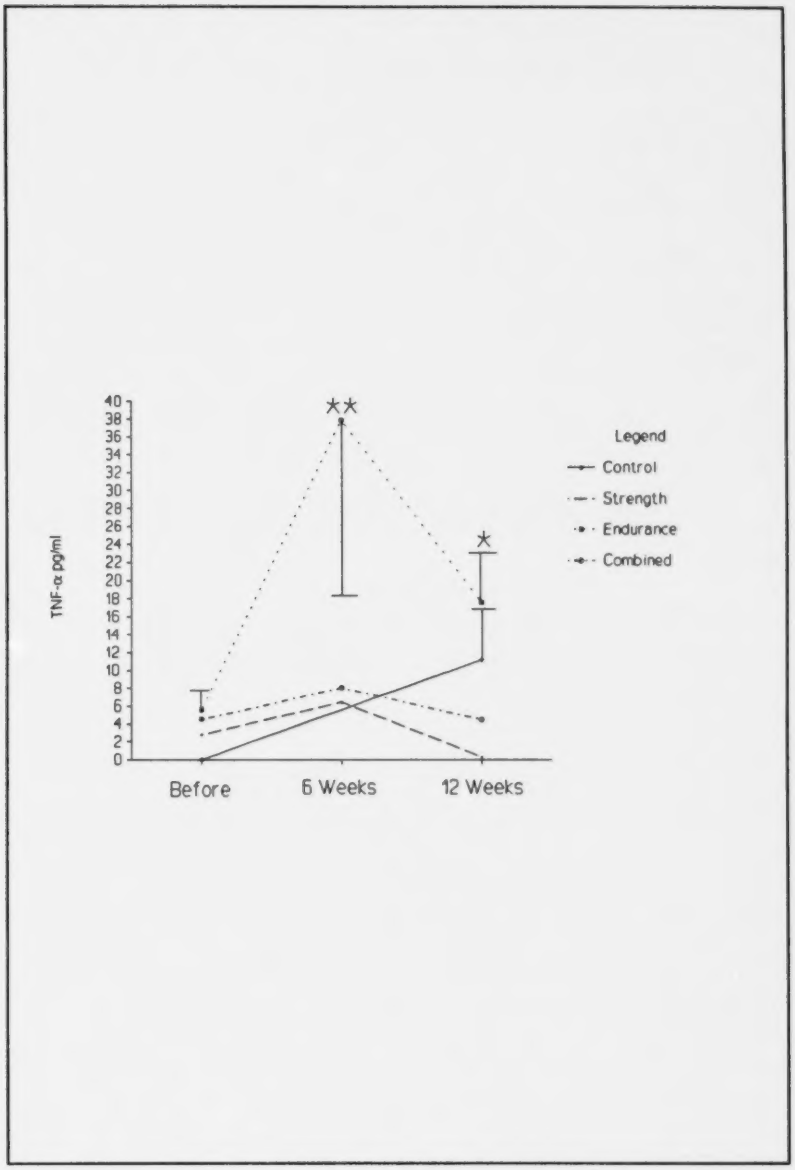

Figure 2-1 Female TNF-α (pg/ml) mean values ± SEM (excluding one value) before, 6 weeks, and 12 weeks of training

** Significantly different from before training, $p < 0.05$

* Significantly different from 6 weeks of training, $p < 0.05$

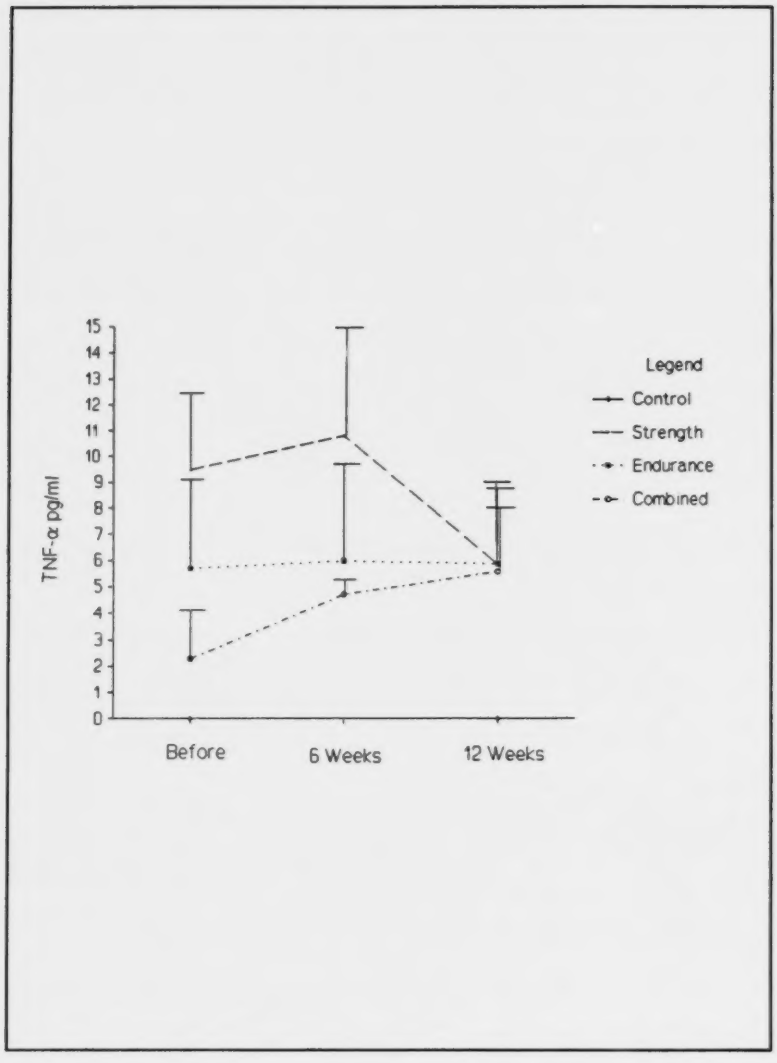

Figure 2-2 Male TNF-α (pg/ml) mean values ± SEM before, 6 weeks, and 12 weeks of training

Note: Male Control Group values 0 ± 0 pg/ml before and after 12 weeks of training.

Changes in TNF-α including the one subject that was excluded from the above data set are represented in Figure 2-3. A significant interaction was observed between both females and males, training groups, as well over time ($F=3.16$, $p<0.05$). Serum TNF-α levels were significantly higher in females than males ($F=6.34$, $p<0.05$). Differences were also observed between the female strength group and the female combined and endurance groups. The female strength only group was significantly different than all training groups and the control group following 6 weeks and 12 weeks of training.

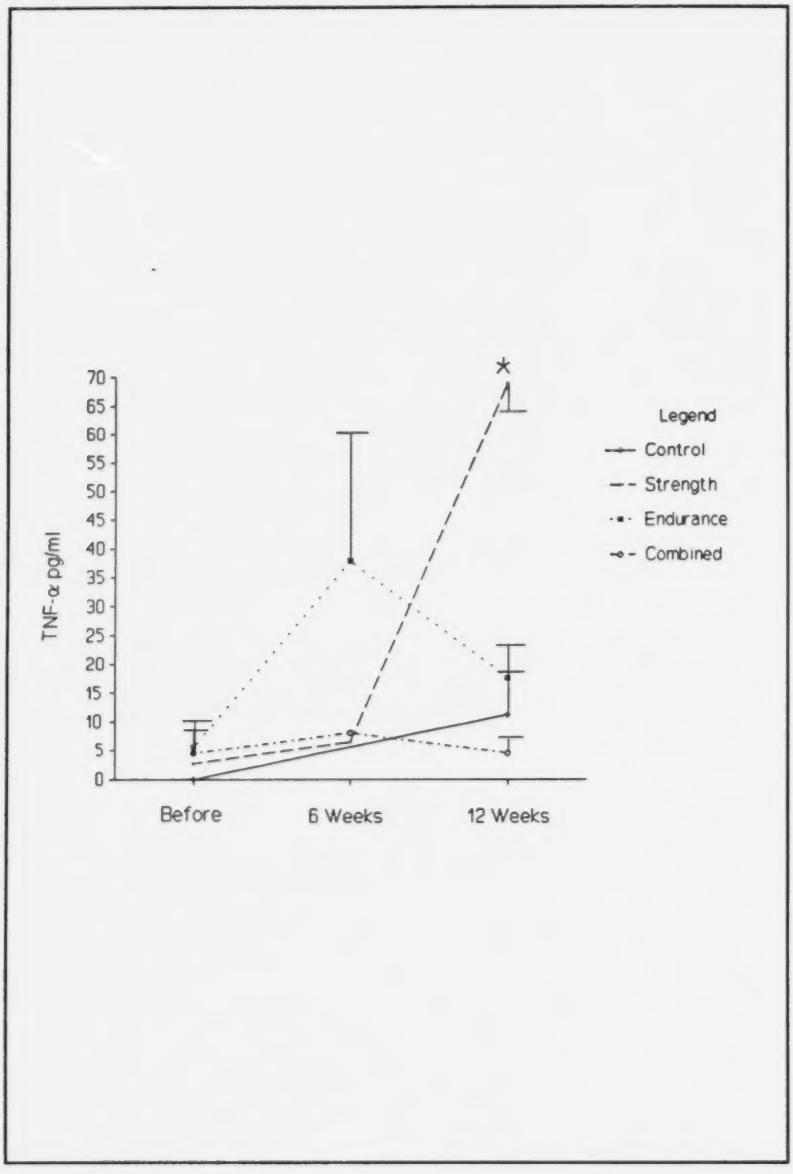

Figure 2-3 TNF-α (pg/ml) mean values ± SEM for all female subjects before, 6 weeks, and 12 weeks of training

* Significantly different from all other training groups following 12 weeks of training.

Testosterone levels are represented in Table 2-3, Figure 2-4, and Figure 2-5. Males were significantly higher than females in all comparisons ($F = 153.75$, $p < 0.05$). Control males had a higher serum testosterone level than all other group both prior to and following 12 weeks of training. This high value obtained before training was an artifact due to random assignment and does not effect the interpretation of the findings because although it was high, it was not significantly different. All training groups did not significantly differ prior to, after 6 weeks, or after 12 weeks of training.

Table 2-2 Testosterone (ng/ml) calculated mean values ± SEM for before, 6 weeks, and 12 weeks of training.

	Before	6 Weeks	12 Weeks
Control Females n=5	.33 ± .06		.50 ± 0.1
Control Males n=5	5.79 ± 1.10*		6.57 ± 1.04**
Strength Females n=3	.28 ± .08	.36 ± .09	.39 ± .07
Strength Males n=7	4.93 ± .40	5.14 ± .30	5.56 ± .73
Endurance Females n=4	.29 ± .04	.55 ± .18	.39 ± .09
Endurance Males n=7	4.93 ± .50	5.26 ± .53	5.53 ± .73
Combined Females n=5	.27 ± .06	.30 ± .07	.28 ± .09
Combined Males n=8	4.74 ± .40	5.45 ± .63	5.73 ± .69

* Significantly different from all other training groups before training, $p < 0.05$

** Significantly different from all other training groups after 12 weeks of training, $p < 0.05$

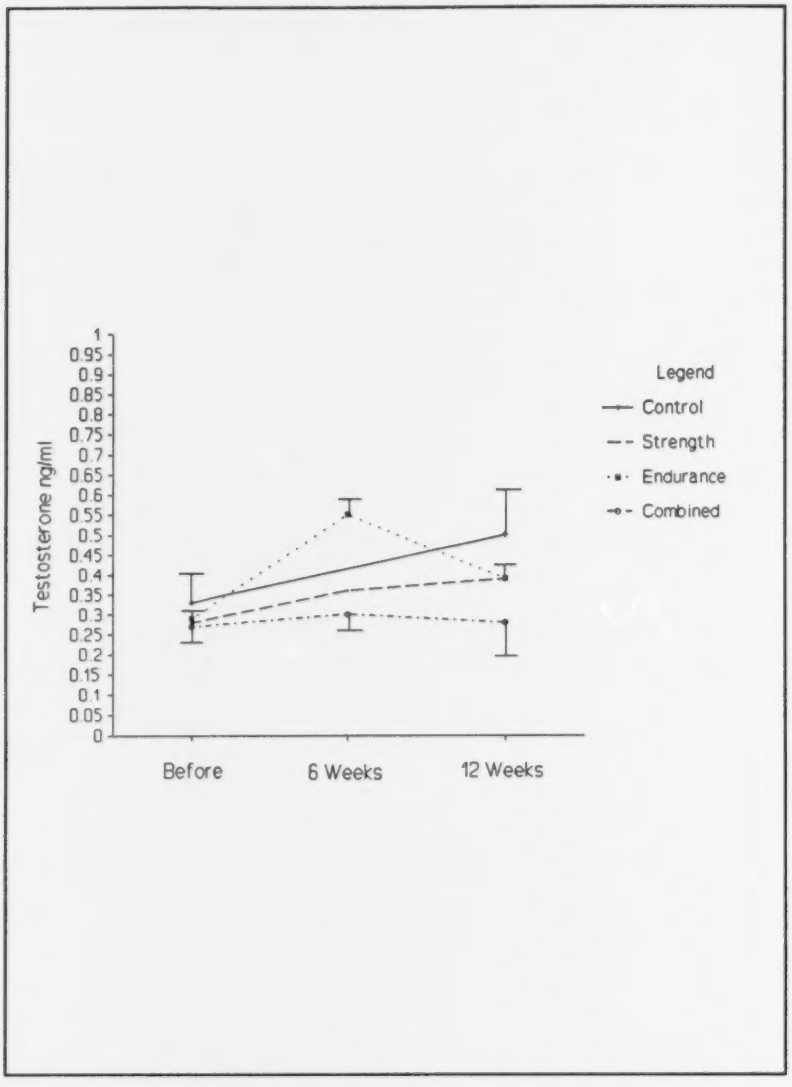

Figure 2-4 Female testosterone (ng/ml) mean values ± SEM before, 6 weeks, and 12 weeks of training

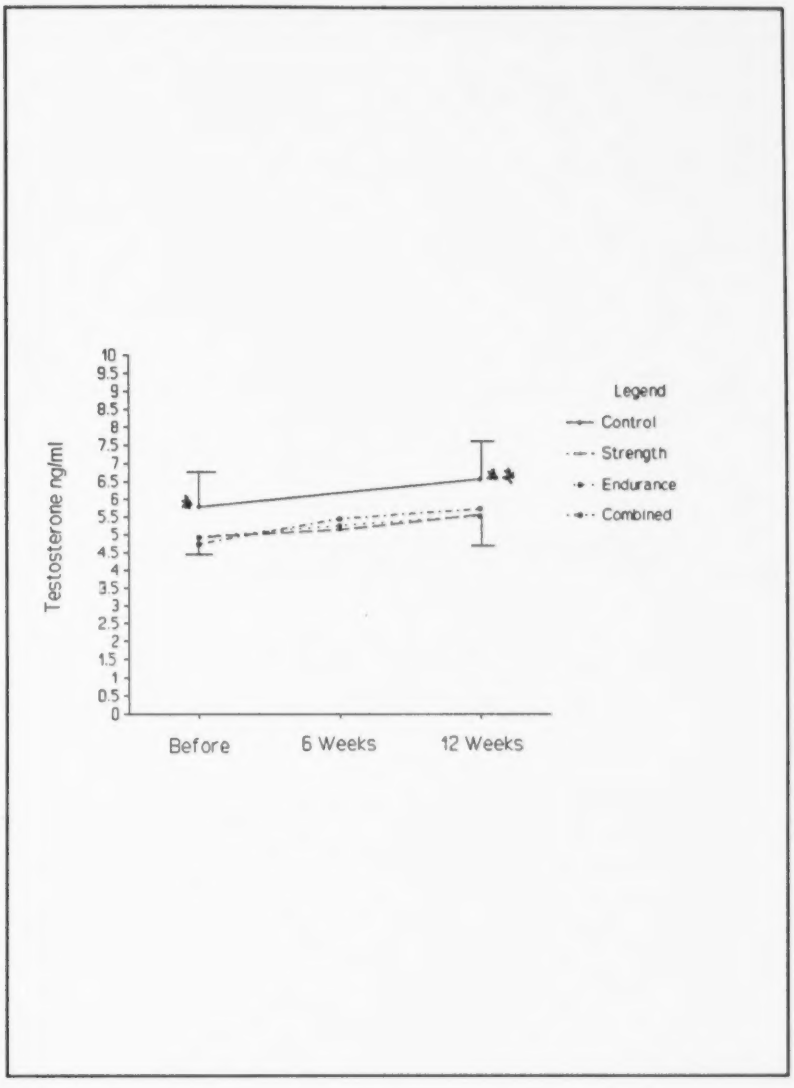

Figure 2-5 Male testosterone (ng/ml) mean values ± SEM before, 6 weeks, and 12 weeks of training

* Significantly different from all other training groups before training, $p<0.05$

** Significantly different from all other training groups after 12 weeks of training, $p<0.05$

Changes in 24 hour urinary cortisol levels are represented in Table 2-3, Figure 2-6, and Figure 2-7. A significant interaction effect was observed between females and males, groups, and following training ($F=3.06$, $P<0.05$). Female subjects had a higher level of urinary cortisol than the males in both the combined strength and endurance group following 6 and 12 weeks of training as well as the control group both before and following 12 weeks of training. Conversely, male subjects had higher values of urinary cortisol in the strength only and the endurance only groups before, and after 6 and 12 weeks of training. The female combined group was significantly higher than the female endurance group. Additionally, the female endurance group was significantly lower than both the strength, and control groups before and after 6 and 12 weeks of training.

Table 2-3 Cortisol (ug/24 hours) calculated mean values ± SEM for before, 6 weeks, and 12 weeks of training.

	Before	6 Weeks	12 Weeks
Control Females n=5	15.35 ± 3.76		14.16 ± 3.09
Control Males n=5	12.91 ± 3.53		12.00 ± 2.94
Strength Females n=3	15.35 ± 7.1	14.04 ± 2.46	14.58 ± 3.64
Strength Males n=7	22.92 ± 6.38	19.06 ± 7.03	22.15 ± 4.22
Endurance Females n=4	11.69 ± 4.12	10.06 ± 2.57	11.57 ± 4.88
Endurance Males n=7	25.42 ± 6.16	20.83 ± 5.72	13.93 ± 3.10
Combined Females n=5	16.42 ± 5.19	23.72 ± 5.17*	30.21 ± 5.56**
Combined Males n=8	19.55 ± 2.53	19.42 ± 3.48	19.42 ± 3.63

* Significantly different from before of training, $p<0.05$

** Significantly different from before training, $p<0.05$

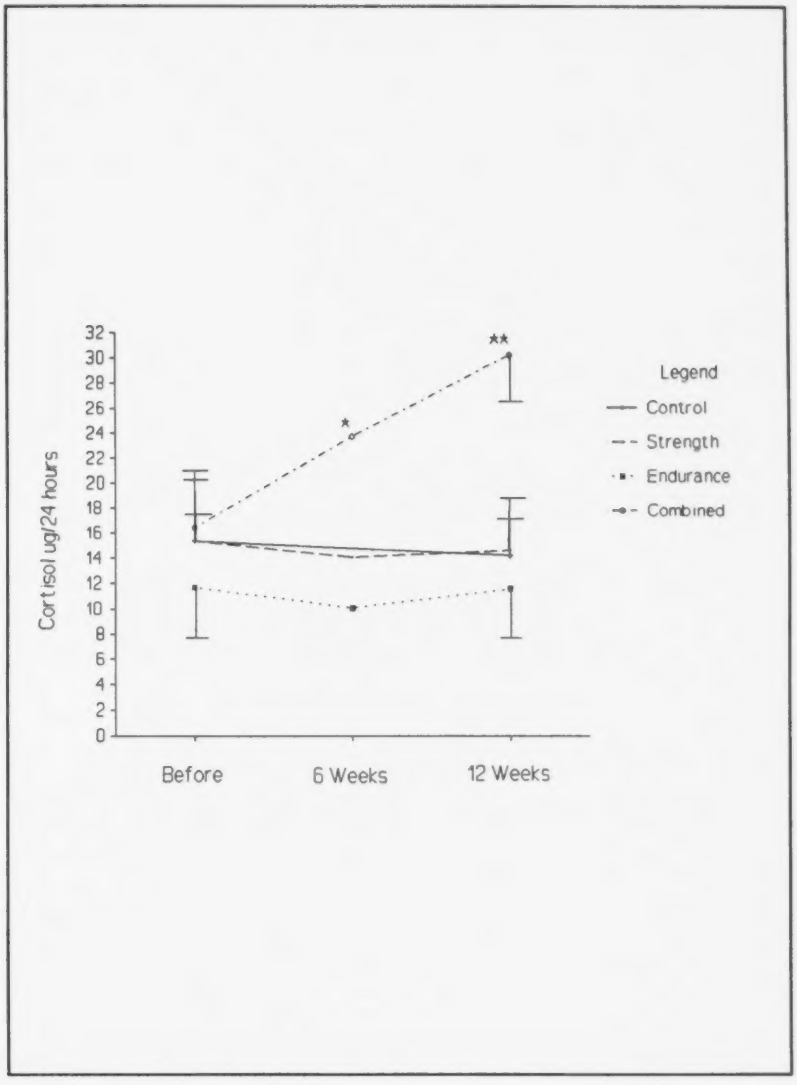

Figure 2-6 Female urinary cortisol (ug/24 hours) mean values ± SEM before, 6 weeks, and 12 weeks of training

* Significantly different from before of training, $p<0.05$

** Significantly different from before training, $p<0.05$

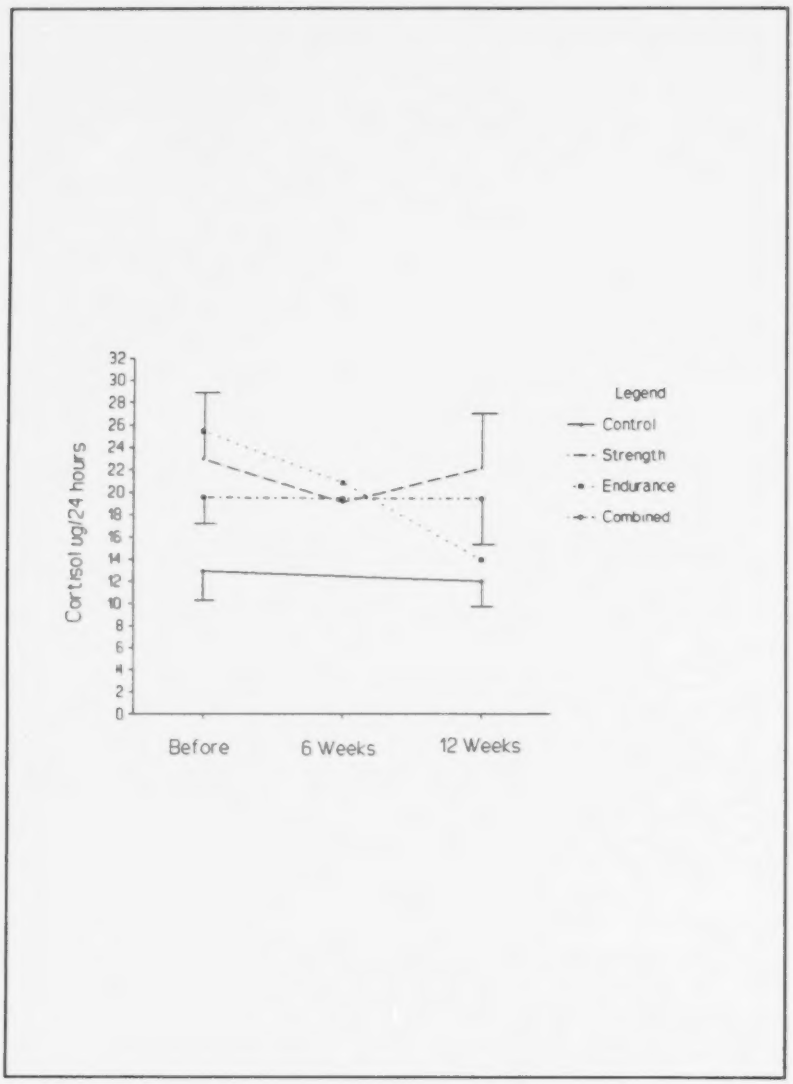

Figure 2-7 Male urinary cortisol (ug/24 hours) mean values ± SEM before, 6 weeks, and 12 weeks of training

Maximal oxygen consumption ($\dot{V}O_2$ max) changes are represented in Table 2-4, Figure 2-8, and Figure 2-9. Both the endurance only and combined strength and endurance groups had significant increases in $\dot{V}O_2$ max following 12 weeks of training ($F=5.34$, $p<0.05$). Relative training increases were similar between both females and males ($F=124.91$, $p<0.05$), although males had a significantly higher absolute VO_2 max when compared to females. The strength only and control group showed no change. The control group had a lower $\dot{V}O_2$ max than all other groups prior to training but again this was an artifact due to random assignment and does not effect the interpretation of the above, because although the value was low it was not significantly different.

Table 2-4 $\dot{V}O_2$ max (l/min) calculated mean values ± SEM for before, after 6 weeks, and after 12 weeks of training

	Before	6 Weeks	12 Weeks
Control Female n=5	2.6 ± 0.13		2.55 ± 0.14
Control Male n=5	3.62 ± 0.3		3.55 ± 0.39
Strength Female n=3	2.8 ± 0.17	2.77 ± 0.28	2.67 ± 0.36
Strength Male n=7	4.35 ± 0.06	4.33 ± 0.06	4.29 ± 0.05
Endurance Female n=4	2.72 ± 0.34	2.96 ± 0.32	3.06 ± 0.30*
Endurance Male n=7	4.32 ± 0.23	4.44 ± 0.23	4.53 ± 0.24*
Combined Female n=5	2.80 ± 0.11	2.9 ± 0.08	3.01 ± 0.09*
Combined Male n=8	4.27 ± 0.18	4.48 ± 0.2	4.47 ± 0.28*

* Significantly different from before training, $p<0.05$

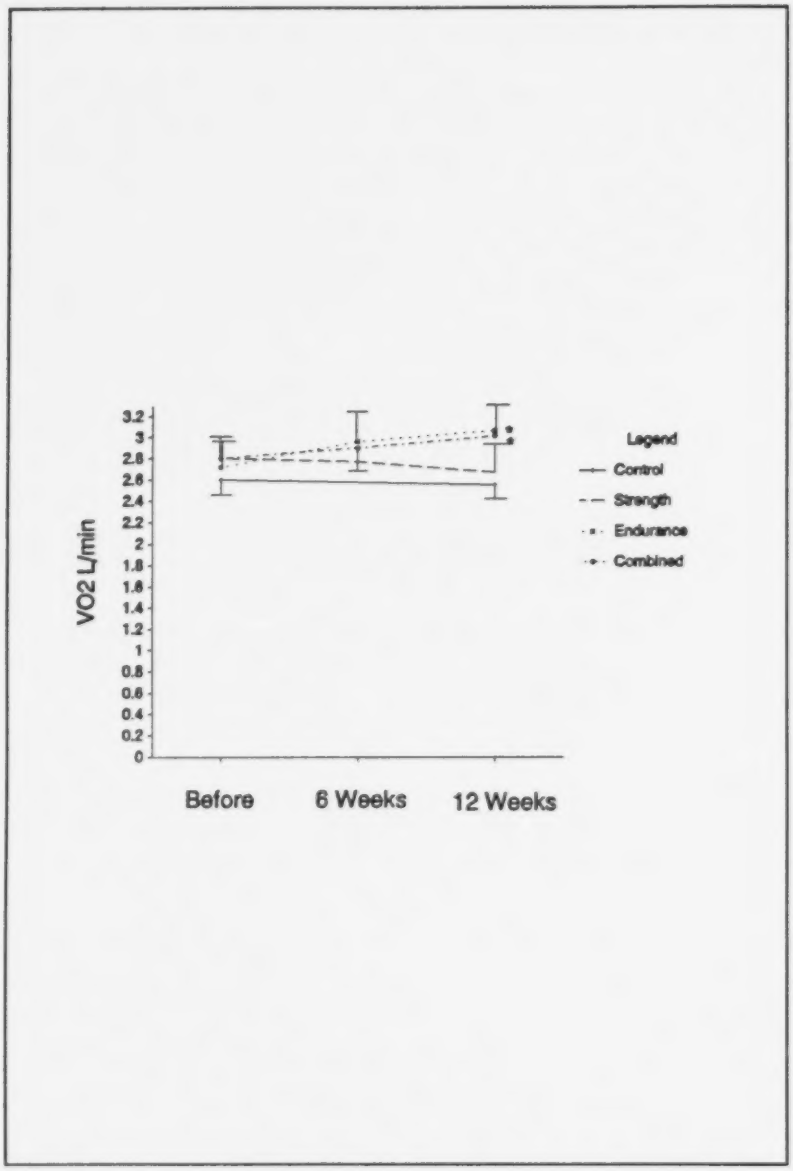

Figure 2-8 Female $\dot{V}O_2$ max (l/min) mean values ± SEM before, 6 weeks, and 12 weeks of training

* Significantly different from before training, $p<0.05$

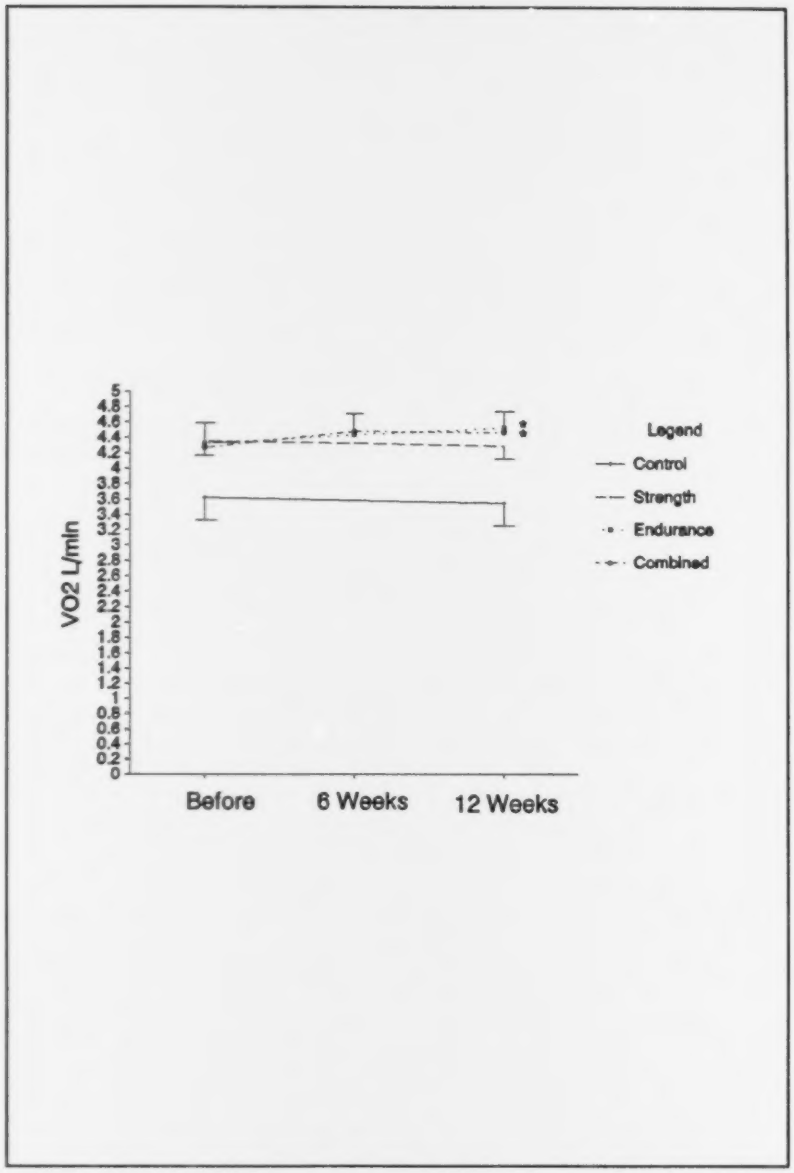

Figure 2-9 Male $\dot{V}O_2$ max (l/min) mean values ± SEM before, 6 weeks, and 12 weeks of training

* Significantly different from before training, $p < 0.05$

Strength changes in unilateral knee extension (1RM) are represented in Table 2-5, Figure 2-10, and Figure 2-11. Both the combined and the strength group showed significant increases in strength both following 6 weeks and 12 weeks of training ($F = 16.86$, $p < 0.05$). However, the strength group had a significantly higher unilateral knee extension 1 RM compared to all other groups following 12 weeks of training. Relative changes in strength were similar between females and males, however males had a greater absolute strength when compared to females. No significant changes were observed in the control group or the endurance only group.

Table 2-5 One repetition maximum knee extension strength (lbs.) mean values ± SEM before, 6 weeks, and 12 weeks of training

	Before	6 Weeks	12 Weeks
Control Female n=5	40.0 ± 4.46		44.0 ± 3.67
Control Male n=5	84.0 ± 8.7		87.0 ± 7.67
Strength Female n=3	37.5 ± 2.5	52.5 ± 4.33*	60 ± 4.56**
Strength Male n=7	81.52 ± 8.11	100.63 ± 7.81*	106.88 ± 8.12***
Endurance Female n=4	42.5 ± 2.5	47.5 ± 4.79	48.75 ± 3.15
Endurance Male n=7	65.71 ± 5.21	85.71 ± 4.68	88.57 ± 4.03
Combined Female n=5	44.0 ± 5.99	55.2 ± 5.78*	62.0 ± 6.43**
Combined Male n=8	78.75 ± 7.18	91.25 ± 5.95*	93.13 ± 6.94**

* Significantly different from before training, $p < 0.05$

** Significantly different from 6 weeks of training, $p < 0.05$

*** Significantly different and higher than all other groups following 12 weeks of training, $p < 0.05$

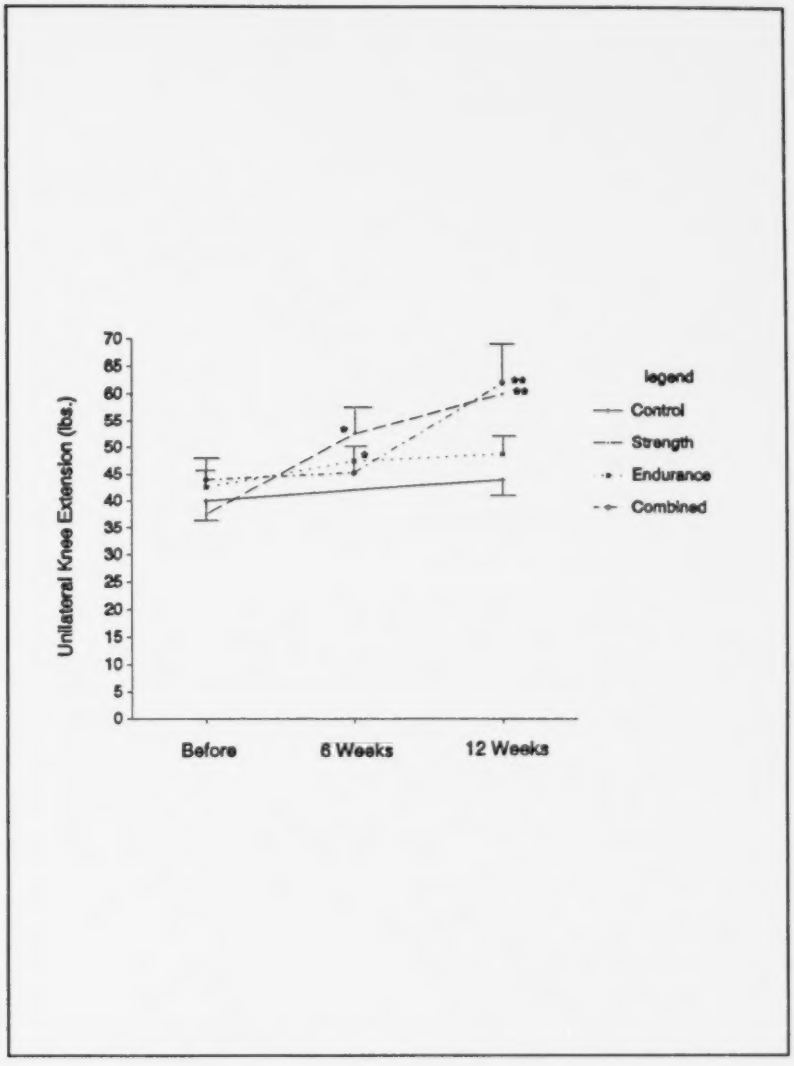

Figure 2-10 Female One repetition maximum knee extension strength (lbs) mean values ± SEM before, 6 weeks, and 12 weeks of training

* Significantly different from before training, $p<0.05$

** Significantly different from 6 weeks of training, $p<0.05$

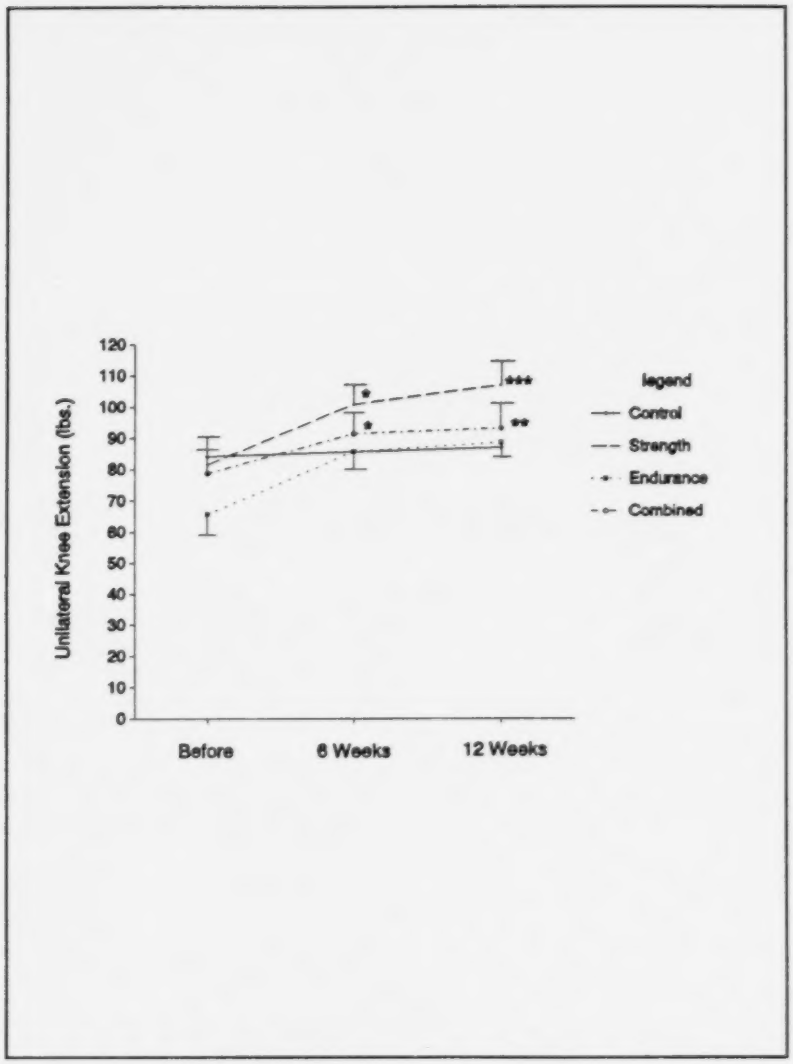

Figure 2-11 Male One repetition maximum knee extension strength (lbs) mean values ± SEM before, 6 weeks, and 12 weeks of training

* Significantly different from before training, $p<0.05$

** Significantly different from 6 weeks of training, $p<0.05$

*** Significantly different and higher than all other groups following 12 weeks of training, $p<0.05$

Discussion

It was the purpose of the present research to evaluate the role of cytokines (TNF-α) and hormones (testosterone and cortisol) in concurrent strength and endurance training. Measurements of TNF-α, testosterone, 24 hour urinary cortisol, $\dot{V}O_2$ max, and knee extension 1 RM were obtained before, after 6 weeks, and after 12 weeks of training in three training groups; strength only, endurance only, combined strength and endurance, and a control group. It was hypothesized that the interaction of cytokine and endocrine parameters may be responsible for a possible antagonism observed during concurrent strength and endurance training (Bell et al., 1992; Hickson, 1980; Dudley and Djamil, 1985; Hunter et al., 1987; Albernethy et al, 1993). The present findings support the existence of a compromised knee extension strength gain but not aerobic endurance ($\dot{V}O_2$ max). However, the underlying reasons for this remain unclear.

Predictable changes were observed as a result of strength training only and aerobic endurance training only. Significant changes in aerobic endurance were observed in both the combined and the endurance groups following 12 weeks of training, but no changes in aerobic endurance were observed in the strength or control groups (Hickson, 1980; Bell et al., 1992; Dudley and Djamil, 1985; Hunter et al., 1987). One RM strength values were significantly increased in both the strength and the combined groups, with the strength group exhibiting the greatest increases. No significant changes were observed in the endurance and control groups. These findings suggest that strength was compromised with combined strength and endurance training, but not aerobic endurance ($\dot{V}O_2$ max) and are concordant with Hickson, (1980), Bell et al. (1992), Dudley and Djamil (1985), Albernethy et al., (1993), and Hunter et al. (1987). Therefore, it appears that an interference effect was present and strength gains in the combined group may have been compromised as a result of the performance of concurrent strength and endurance training.

No significant changes in serum testosterone levels were observed in the present investigation in male or female subjects in any of the training groups. The lack of change in serum testosterone levels would suggest that the physical training (strength, endurance, or combined strength and endurance) did not induce an anabolic state in skeletal muscle. The level of serum testosterone (or a lack of) has been indicated to play an important role in determining the adaptations and the recovery of skeletal muscle tissue to training (Kraemer, 1988). The role of testosterone is characteristically anabolic, aiding with protein synthesis and tissue growth (Kuppasalmi and Aldercrutz, 1985; Hakkinen, 1989; Hackney, 1989; Kraemer, 1991). Hence, this may suggest that there may have been a lack of skeletal muscle protein synthesis which in turn could lead to a lack of change in muscle size and strength. However, strength parameters increased in the combined group and the strength group despite the lack of change in serum testosterone in the present investigation. Increases in strength are usually accompanied by increases in muscle protein synthesis (Kraemer, 1988) and as a result muscle size and strength. This suggests that the skeletal muscle tissue of subjects in the combined and strength groups was in an anabolic state despite the lack of change in serum total testosterone. Additionally, only the measurement of total testosterone was made in the present investigation. Thus, one must consider that the measurement of total testosterone may not be reflective of the "biologically active" portion of serum testosterone, and in turn subsequent changes as a result of training. Additional measurement of SHBG (sex hormone binding goblin) could determine changes in the bound versus free ratio of testosterone, thus helping to determine the change of the biologically active portion testosterone in the interference effect (Kuppasalmi and Aldercrutz, 1985).

The female combined group had the highest urinary cortisol response (30.21 ug/24 hours) in comparison to all other training groups. The hypercortisolic state of the female combined group may be indicative of a catabolic environment which may inhibit muscle protein synthesis (Goodman, 1993). Thus, increased

levels of urinary cortisol could be a contributing factor to the compromised strength gains observed in the female combined group. However, the present study did not determine changes in muscle protein regulation or muscle fiber size. The catabolic role of cortisol does not explain the underlying reasons for the compromised strength gains in the male combined group due to the lack of change in levels of urinary cortisol over the training period. Further research is necessary to determine the underlying reason for this gender difference and the consistent compromise of strength gains in both males and females with concurrent strength and endurance training.

The female endurance group had the highest circulating TNF-α levels (17.59 pg/ml) in comparison to all other male and female training groups. Male subjects in all training groups showed no significant changes in TNF-α following training. Thus, differences in circulating TNF-α levels following training were significant only in the female endurance group and not in any other male and female training groups. It appears that strength training and concurrent strength and endurance training do not significantly influence or change the expression of circulating TNF-α in male or female subjects. The above indicates that TNF-α may not influence the interference effect observed following concurrent strength and endurance training. But, despite the lack of change in circulating TNF-α levels following training, consideration must be given to the interaction existing between TNF-α and glucocorticoids (cortisol) identified by Goodman (1993). As stated above, female subjects in the combined group had a significantly increased level of urinary cortisol following training. Goodman (1993) has found that TNF-α and glucocorticoids participate together to inhibit muscle protein synthesis. Findings in Goodman's (1993) laboratory indicate that TNF-α orchestrates the muscle proteolytic response and glucocorticoids act as the causative catabolic agent regulating protein synthesis. Thus, TNF-α may act as a precursor to cortisol, and the combined effect of the two catabolic agents may be the inhibition of

muscle protein synthesis. Thus, both glucocorticoids and TNF-α may still play a role in the enhancement of muscle proteolysis associated with the interference effect.

It is important to note that the above is applicable to the female combined group due to the high levels of urinary cortisol. Compromised strength gains in the male combined group can not be explained. Further research is required in this area.

In summary, concurrent strength and endurance training resulted in compromised strength gains and an interference effect. However, gains in aerobic endurance ($\dot{V}O_2$ max) were not affected in either male or female subjects. The above may be partially explained by elevated levels of glucocorticoids (cortisol) in female subjects. However, male subjects did not elicit a significant cortisol response, thus the underlying reason for the compromise in strength gains in male subjects can not be explained.

The interference effect observed with the compromise of strength gains in both female and male subjects can not be attributed to interactions between hormonal and immune parameters in response to exercise based on the present study. There appears to be no clear relationship between compromised strength gains and the interaction between anabolic (testosterone), catabolic (cortisol), and cytokine (TNF-α) responses with training. Future research is required in the area to determine the underlying reasons of the interference effect and the compromise of strength gains but not aerobic endurance ($\dot{V}O_2$ max) during concurrent strength and endurance training.

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Appendix A

Review of Literature

The purpose of the following review was to delineate the roles, production, and secretion of testosterone, cortisol, and TNF-α and their respective interactions with each other, and with protein synthesis in skeletal muscle in response to exercise induced stress. The implications derived from this investigation were intended to focus on the possible interaction between immune and hormonal parameters in producing the interference effect observed as a result of concurrent strength and endurance training, and consequent overtraining.

Testosterone

Testosterone is an anabolic and adrenergic hormone that stimulates skeletal muscle protein synthesis. This hormone is responsible for the development of growth in puberty and the secondary sexual characteristics of males. Testosterone in the male is responsible for the initiation of the growth spurt during puberty, and also the subsequent cessation of growth by the closure of epiphyseal growth plates. Testosterone also functions by stimulating haematopoiesis and increasing glycogen synthesis and storage (Kuoppasalmi & Adlercreutz, 1985). Mature males, as well as females have detectable levels of plasma testosterone. However, the amounts circulating in the normal female are less or lower than in the male.

The primary source of testosterone in the male is the testis. It is secreted in amounts ranging from 4-10 mg/day (Cumming et al, 1989; Hackney et al, 1989). The secretion pattern is episodic and follows the individual's circadian rhythm, reflecting a low circulating level in the late afternoon and a relatively high plasma testosterone level in the morning.

The adrenal cortex is the secondary source of testosterone in the male and the primary source of testosterone in the female. The adrenal cortex is known to be a multi-functional organ because it is responsible for both the production and secretion of testosterone as well as an additional 40 hormone substances (Johnson, 1992).

In the female, testosterone exists in lower concentrations, but as in the male, functions in protein synthesis, muscle repair, and growth. The predominant steroid hormone of the female is estrogen, and its primary source is the ovaries. Like testosterone in the male, estrogen in the female is responsible for the development of secondary sex characteristics and the onset of puberty and the menarche. However, testosterone is also found in the plasma and is produced and originates primarily from the peripheral conversion of steroid precursors (Kuoppasalmi & Adlercreutz, 1985).

In both males and females, testosterone in the blood exists in free and bound forms. The free component of plasma testosterone is very small, comprising only approximately 2-3% of the total circulating level of the hormone. Although the amount of free testosterone present in the blood is small, this is the biologically active portion. In contrast, the bound portion of plasma testosterone binds to albumin (30-40%)(Johnson, 1992; Kuoppasalmi & Adlercreutz, 1985) and to sex hormone binding globulin (SHBG) (56%) (Kuoppasalmi & Adlercreutz, 1985). Total testosterone is a combination of the free and bound portions of circulating testosterone.

SHBG is a glycoprotein that binds both estrogen and testosterone, but its single binding site has a higher affinity for testosterone. Its concentration in plasma is increased by estrogens and decreased by androgens. Thus, SHBG is more abundant in the female than in the male (Johnson, 1992). The physiological importance of testosterone binding to SHBG is illustrated by the influence it has

on the free testosterone level and the metabolic clearance rate (MCR) of the hormone. Testosterone is primarily metabolized in the liver, but also approximately half of the hormone is metabolized extrahepatically by the kidneys, lungs, adipose tissue, and skeletal muscle (Kuoppasalmi & Adlercreutz, 1985).

The Role of Testosterone in the Human Body

It has been established that testosterone plays an integral role in androgen-dependent skeletal muscle hypertrophy and is synergistic with growth hormone. Testosterone binds and acts directly on the muscle via specific receptors. One of its physiological roles is in the prevention of muscle degradation associated with high volume and high intensity training. An increase in the utilization of testosterone appears to be important in maintaining the integrity of muscle in chronic exercise training at high intensities and volumes. Both Cumming et al. (1989) and Fry et al, (1991), state that it is possible that one of the consequences of high intensity endurance training or interval anaerobic training regimes could be muscle damage and decreased muscle hypertrophy due to inhibition of protein synthesis as a result of suppressed circulating testosterone levels. Additionally, the catabolic effects of high cortisol levels could also contribute to the inability of testosterone to prevent muscle catabolism. Elevated cortisol concentrations suppress testicular steroidgenic processes and thus reduce the serum testosterone concentrations (Fry et al, 1991; Cumming et al, 1989). Further testosterone serves to offset the catabolic functions of cortisol, and depressed testosterone concentrations may therefore hinder the repair of muscle damage associated with high intensity physical activity (Fry et al, 1991; Cumming et al, 1989). Elevated cortisol concentrations detected immediately following high intensity training may therefore contribute to muscle catabolism when coinciding with depressed testosterone serum levels. Cortisol-mediated catabolism may be accelerated if the high intensity training is repeated prior to full recovery of normal testosterone levels. This could be one possible mechanism leading to overtraining or the

interference effect observed in concurrent strength and endurance training regimes. This explanation seems viable since the muscles are provided with little opportunity to regenerate and are under constant catabolic stress (Fry et al, 1991).

Further, it has been speculated that androgens may play an important role in the maintenance and effectiveness of the immune system (Cumming et al., 1989; Fry et al, 1991). However, it is also well established that other hormones such as cortisol (glucocorticoids) play an prominent role in the suppression of the immune system.

General Response of Testosterone to Exercise

In general, there is an increase in circulating testosterone with maximal or near maximal short exercise bouts, while submaximal longer duration exercise appears to decrease circulating levels of testosterone. (Cumming et al, 1989; Fry et al, 1991; Hackney, 1989). Cumming et al, (1989) reported suppressions of testosterone concentrations for several days following long duration, submaximal activity. Shorter duration, high intensity anaerobic exercise has elicited reductions in circulating testosterone concentrations for at least 24 hours. It is possible repeated intensive high intensity work sessions may result in persistent depression of testosterone levels (Fry et al, 1991). This is consistent with Cumming et al (1989) who stated that androgen levels continue to be depressed for an extended period of time following the completion of training sessions (Cumming et al, 1989).

Determinants of Circulating Levels of Plasma Testosterone

Circulating levels of plasma testosterone are affected by multiple factors which alter the mechanisms responsible for hormone production, secretion, and utilization. The circulating level of plasma testosterone in the human reflects the amount of testosterone being produced and secreted, verses the amount of testosterone being metabolized and cleared from the blood. The rate of these

processes can be affected by changes in the physiological state of the subject. Exercise and physical training of various intensities and durations are capable of changing the homeostasis of the body, and thus altering the metabolic turnover of circulating levels of plasma testosterone (Hackney, 1989).

Cumming et al. (1989) propose two mechanisms to explain alterations in testosterone production namely central and peripheral mechanisms. It is believed that the primary mechanism affecting testosterone production is central in nature. The production of testosterone is directly related to the action and availability of luteinizing hormone (LH) released from the pituitary gland. As the level of LH increases, so does the level of testosterone. The influence of LH along with gonadotrophin-releasing hormone (GnRH) is the central (specific) mechanism which induces production. Thus, abnormalities in the release of LH could be responsible for reductions in testosterone production associated with chronic training. Evidence of continued low levels of testosterone unassociated with an increase in LH implies that the central control is not absolute (Wheeler et al, 1991).

Peripheral (non-specific) mechanisms that regulate testosterone levels include metabolic clearance rates and plasma volumes. Another factor responsible for depressed levels of testosterone is enhanced activity of the ACTH-cortisol axis. Studies have shown that chronic elevations of serum cortisol shift the cortisol/testosterone ratio, and in turn affect both muscle catabolism and testosterone production (Cumming et al. 1989; Wheeler et al, 1991).

Secretion of testosterone in the male is affected by blood flow to the testes, because testosterone is freely diffusible and fat soluble. Additionally, the testes are not capable of storing the hormone and consequently, exercise influences secretion via changes in blood flow. Catecholamines also appear to play a role because they are altered with exercise (elevated) and affect blood flow. The

secretion of testosterone varies with both vasoconstriction and vasodilation. High plasma catecholamine levels stimulate testicular testosterone secretion. On the other hand, high glucocorticoid levels depress plasma testosterone levels.

A decrease in testosterone level results from a number of factors including decreases in the rate of production, decreased protein binding, and increased clearance. Any of the above factors alone or in combination may cause a reduction in androgen levels. Hackney (1989) cautioned that observed changes in blood levels of a hormone may not necessarily reflect alterations in production, secretion, or metabolic clearance rates. Rather, this may more accurately indicate that testosterone may be binding to protein carriers, or that an increase or decrease in plasma protein concentration or volume may have occurred. When the total plasma volume decreases hormonal substances becoming more concentrated, or when the plasma volume increases the hormone becomes diluted. These changes do not reflect a true change in hormonal concentration, or in the metabolic clearance rate of the hormone (Hackney, 1989).

Effects of Endurance Training on Testosterone Levels

The physiological changes that occur in both men and woman in response to endurance training are reported to be similar, and hence circulating levels of gender specific androgens are similarly affected. In the literature, different results have been reported regarding the response of testosterone blood levels to endurance based exercise. It is important to note that the corresponding changes in testosterone levels are primarily dependent on the physiological demands of the training session. There is an observed consistent reduction in circulating levels of testosterone following long duration submaximal exercise in males. Accordingly, it is believed that an extended suppression of circulating testosterone occurs with prolonged endurance training (Cumming et al., 1989). This reduction in level of circulating hormone appears to be correlated with the intensity and duration of the athletes training load. Reports from different laboratories vary and indicate

discordant results depending upon the characteristics of the training sessions. Testosterone concentrations increase after training sessions lasting less than 2 hours and decrease if the sessions last longer than three hours (Guglielmini et al., 1984; Cumming et al., 1989; Jensen et al., 1991).

In accordance with the above, Jensen et al. (1991) reported a 37% increase in testosterone concentrations following a 90 minute endurance training session. The elevation in concentration was transient and returned to a resting level 2 hours post-exercise. The post-exercise level and the morning resting concentration level observed on a rest day were not significantly different. In studies conducted by Hakkinen et al. (1988); MacConnie et al. (1986); and Kuppasalmi (1980), testosterone concentrations were reported to be unchanged or decreased when measured in the 30 - 60 minutes following a single bout of exercise regardless of the type of training. The above results indicate that under normal training conditions, testosterone concentrations return to resting concentrations rapidly.

Hakkinen et al. (1988) and Urhausen et al. (1987) have both reported decreased concentrations of serum testosterone following 2 hour training sessions twice per day, or on successive days of hard training, respectively. Further, Wheeler et al. (1986) reported a lower mean serum testosterone level in runners with a training program over 65 km/week, but runners running less than 65 km/week were not significantly affected. Prospective studies have confirmed that endurance training and other forms of strenuous training can result in reductions of both free and non-specifically bound testosterone (SHBG) (Cumming et al.,1989).

In summary, the response of testosterone blood levels and the resulting post-exercise concentration levels are variable depending on the duration, type, and intensity of the training session.

Effects of Strength Training on Testosterone Levels

In strength trained athletes with a long training background and with a high volume of training, the role of endogenous hormone balance may be important for strength development. During the most stressful training weeks of prolonged strength training, the level of biologically active unbound testosterone as well as the balance between the androgenic-anabolic activity and the catabolizing effect of glucocorticoids, may be of great importance for the training of muscular strength (Hakkinen, 1989).

Similar to submaximal prolonged endurance training and near-maximal or maximal training, it is also known that the adaptive responses in the endocrine system to strength training, are also dependent upon the duration and intensity of the training stimulus. The hormonal adaptations that result from short and long term strength training are distinct, but also vary depending on the type of activity and the musculature utilized. Short term strength training regimes have elicited only minor changes in serum levels of androgens, but prolonged strength training characteristically induces changes which include an increase in serum levels of testosterone (Hakkinen, 1989). Kraemer (1988) suggests that increased concentrations of testosterone following an acute bout of weight lifting may be related to the intensity and volume of the training session, as well as the amount of muscle mass used. Further, Schwab et al. (1993) have also suggested that there may be a critical threshold level of intensity and volume that dictates the presence of altered concentrations of testosterone. This would suggest that there is a distinct workload that when met and exceeded, elicits an increase in testosterone. It has been suggested by Kuoppasalmi et al. (1985) that the strength gains are not a direct result of the enhanced androgen levels. Rather, gains during intensive training might be directly related to the possible periodical deficiency of testosterone during vigourous training periods (Kuoppasalmi et al, 1981). Thus, it appears that the suppression of these substances plays a more integral role on performance and strength. This finding agrees with those of Hakkinen and

associates (1989). The investigators reported similar findings in which a slight increase in serum testosterone/cortisol ratio was observed during a 6 month training period. It was reported that during the last vigorous, high intensity training month, individual changes were varied in both strength gains and in the testosterone\cortisol ratio. During this time period, some of the subjects were able to increase their strength, while others actually may have decreased slightly. Individual changes occurred concurrently with the changes observed in both the serum testosterone and cortisol responses, as well as in the resulting ratio. This suggests that the balance between the serum testosterone/cortisol ratio, and in turn the balance between androgenic-anabolic activity and the catabolic effects of glucocorticoids during prolonged training, is of particular importance. The apparent relationship between the above hormones, and alternate fluctuations of these factors have direct effects on strength gains. One could speculate from the above findings that the alterations and subsequent changes in the serum testosterone : cortisol ratio have a direct effect on protein synthesis and muscle degradation.

Differing Effects of Strength and Endurance Training on Plasma Testosterone

Jensen et al. (1991) investigated male subject's acute testosterone response to single bout strength and endurance training sessions. The study indicated that there were no significant differences in testosterone concentrations immediately following the training session, or in the hours following. However, Jensen and associates (1991) indicate that there are large differences in the muscle adaptation to strength and endurance training. Endurance training is a poor stimulus for muscle hypertrophy (Howald et al, 1985; Ingjer, 1979; Jensen et al, 1991), while strength training performed at 80% of one repetition maximum is known to increase muscle mass (McDonagh and Davis, 1984). The differences in muscle adaptation should reflect the role of testosterone (Cumming et al., 1989; Knoppasalmi and Aldercreutz, 1985; Johnson, 1992) and the effect it has on protein synthesis and muscle hypertrophy. The lack of reported differences in

testosterone concentrations by Jensen et al. (1991) following single bout strength and endurance session does not indicate that testosterone is an unimportant factor in muscle adaptation associated with diseparate forms of strength and endurance training. Rather, these results may suggest that the role of testosterone in muscle adaptation may be one of a longer term training response. Kraemer (1988) suggested that observed tissue adaptations following exercise are dependent upon the intensity, type, and duration of the activity. Additionally, tissue adaptation is dependent upon the hormonal response of the body and the resulting homeostasis (Kraemer, 1988). Thus, the role of testosterone in muscle adaptation to disseparate forms of exercise is multi-dimensional and specific to the stress imposed.

Gender Differences

Of the available literature, a limited number of studies have investigated testosterone responses to strength training, and fewer to endurance training. The majority of endocrinological based studies utilizing female subjects have examined menstrual dysfunction and related factors. Thus, most of the available literature on testosterone has solely focused on changes in male subjects. Accordingly, only a few investigators have devoted research projects solely to the investigation of the testosterone response of female athletes. However, recently Kraemer et al. (1993) examined the independent influence of resistance training and rest period length on serum hormone concentrations in women. Previous to this investigation, very few studies focused on hormonal changes relating to chronic or acute heavy resistance exercise and females. Research conducted by Kraemer et al. (1993) indicated that changes in testosterone concentrations with heavy-resistance exercise have been possible, but the majority of muscle adaptation is attributed to higher secretions of adrenal and androgenic hormones in some women. Kraemer et al. (1993) state that in most women, exercise induced elevations of serum testosterone are not common. Rather, the level of testosterone remains at a resting level with minimal increases. As indicated, this factor suggests that other

anabolic hormones such as growth hormone and growth factors are responsible for the exercise-induced adaptations observed in training female athletes. The anabolic adaptive mechanism related to protein synthesis and muscle growth remain to be fully defined and explained. Additionally, the influence of hormonal substances such as testosterone, and the mechanisms, pathways, and interactions that influence the pathway are still to be completely identified.

Kraemer et al. (1993) reported on distinct gender differences in hormonal response with two different exercise protocols. It is speculated that the differing hormonal responses between males and females could be attributed to a lack of a testosterone response in the females, as well as to a higher concentration of growth hormone in the early follicular phase of the menstrual cycle. The above investigation demonstrated that strength training did not elicit a significant testosterone response; however, there were marked increases in cortisol and growth hormone.

Kraemer et al (1993) caution that one must consider both the phase of the woman's menstrual cycle as well as the exercise protocol when examining hormonal responses to exercise and the role testosterone plays in muscle remodelling. In this study (Kraemer et al, 1993), none of the female subjects presented elevated serum testosterone concentrations. It is uncertain what factors dictate acute or chronic alterations in testosterone levels in the training female. However, it is known that observed changes in testosterone levels may be dependent on larger contributions from the adrenal cortex (Kraemer et al, 1993). Additionally, Kraemer et al. (1993) state that obvious individual differences are seen in training females and therefore in muscle adaptation.

Some investigations have referred to conflicting results in females regarding the response of testosterone levels to exercise. For example, Cumming et al. (1987) reported that small increases in serum testosterone may be possible

in some women, but Kraemer et al. (1993) reported conflicting results indicating that there are no alterations reported with acute exercise or training. In women, it appears that other endogenous anabolic hormones play a more significant role in physiological adaptations to training.

Cortisol

Cortisol is the predominant glucocorticoid in man, and thus the most investigated and discussed in the current literature (Kuppasalmi and Adlercrutz, 1985; Brandenberger, 1985; Johnson, 1992; Kraemer et al., 1993; Schwab et al., 1993). Glucocorticoids produce a number of diverse physiological actions and affect many tissues of the body. Each target tissue responds specifically to either an excess or deficiency of glucocorticoids. It has been stated that high concentrations of glucocorticoids inhibit protein synthesis and promote the rapid breakdown of muscle and lymphoid tissue that serve as reservoirs for stored proteins (Tawa and Goldberg, 1986). Since exercise and high intensity training are known to cause an increase in circulating glucocorticoids, it is important to investigate and understand the acute and chronic response of blood cortisol levels to various modes of training.

The Role of Cortisol in the Human Body

Cortisol is secreted from the adrenal cortex intermittently in amounts ranging from 10-20 mg/day under normal resting conditions. The release of cortisol is preceded by a secretion of ACTH from the pituitary gland (Brandenberger, 1985). The secretion of ACTH is related to alterations in the homeostasis of the subject and in response to the surrounding environment. The response of blood cortisol levels to physiological alterations of homeostasis have been attributed to the activation of the hypotalamo-pituitary-adrenocortical system (Kuoppasalmi and Adlercreutz, 1985). Cortisol levels are elevated in response to stress caused by physiological and psychological factors including both trauma and perceptions of stress on the body or from the surrounding environment. Such

stress is commonly the result of physical activity and exercise. Physical exercise of sufficient intensity and duration elicits the hormonal changes typical of the stress response. In humans, it appears that the cortisol response is not uniform (Kuoppasalmi and Adlercreutz, 1985), rather it is dependent upon a number of factors which influence the activation of the pathway.

The pathway responsible for the release of cortisol in response to exercise stress is not well defined, but it appears that the mechanism associated with activation may be neurogenic or systemic. Secretion of cortisol possibly results from humoral or psychic factors which stimulate ACTH secretion and cortisol is regulated by the secretion of ACTH from the anterior pituitary. ACTH alters the response of the adrenal cortex and in turn, the circulating levels of cortisol. The concentration of cortisol is decreased in the absence of ACTH, and correspondingly increases when ACTH levels become elevated. The secretion of ACTH is dependent upon vascular contact between the anterior lobe of the pituitary gland and hypothalamus and is driven by corticotropin-releasing hormone (CRH). ACTH release is also dependent upon a negative feedback system which regulates the level of cortisol secretion by monitoring the circulating concentrations. Following the stimulation of the adrenal cortex with ACTH, cortisol is released which in turn, inhibits further secretion of the hormone by the anterior pituitary (Johnson, 1992).

ACTH and the level of cortisol in the blood are not constant, being somewhat episodic and similar to the secretion pattern of testosterone. It has been established that ACTH and cortisol concentrations in the blood plasma fluctuate and parallel circadian rhythms and physical activity patterns. Hormone levels are highest in the early morning and lowest in the evening. Although cortisol is elevated to its greatest concentration in the morning, the levels of circulating

hormone are precisely controlled during the day in response to both physiological and psychological stress endured by the subject (Johnson, 1992; Sutton et al, 1990; Kuoppasalmi and Adlercreutz, 1985).

It has been shown that cortisol levels fluctuate during the day in response to food ingestion. There are two notable peaks which correspond to eating and thus are termed meal-related peaks. Accordingly, there is a mid-day peak which parallels the noon meal, and another at 2000 hours that corresponds to the evening meal (Sutton et al., 1990; Kuppasalmi and Adlercrutz, 1985).

In addition to the above identified factors, ACTH and related cortisol secretion are also affected by immune parameters. Johnson (1992) states that humoral mediators of the immune system, including cytokines can directly affect the secretion of ACTH and in turn cortisol. Because glucocorticoids inhibit cytokine production, it is speculated that there may be some humoral communication between the cells of the immune system and the adrenal cortex (Harbour-McMenamin and Blalock, 1989; Wicks et al., 1992; Esperson et al., 1991; Vailas et al., 1991; Goodman, 1993; Gilbert and Payan, 1991). The net result of the interaction has not been fully established.

Cortisol, like testosterone can be bound in blood to plasma proteins. Approximately 60% is bound to cortisol-binding goblin (CBG) and the remaining portions are either bound to albumin, or unbound (Kuppasalmi and Adlercrutz, 1985). The albumin-bound portion of cortisol is very small and the binding capabilities are limited. Like the unbound portion of testosterone, the unbound portion of cortisol is also the biologically active portion which affects target cells and organs (Kuppasalmi and Adlercrutz, 1985).

The influence that cortisol elicits on protein synthesis and muscle in relation to exercise and training, is not fully understood. However, extensive research has been conducted in various laboratories looking at the possible effects of hormonal response, secretions, and effects on training. Tawa and Golberg (1986), Sutton et al.,(1990), Johnson (1992), and Kuppasalmi and Adlercrutz, (1985) have stated that glucocorticoids such as cortisol, decrease muscle size by retarding growth and acting to promote the release of amino acids from muscle. Tawa and Golberg (1986) hypothesize that the mechanisms of growth retardation include the decreased expression of DNA and protein synthesis, as well as reduced amino acid uptake by the muscle cells. These growth limiting effects are seen with normal circulating levels of cortisol. Kraemer et al. (1993), Sutton et al. (1990), and Kuppasalmi and Adlercrutz (1985) have suggested that exercise, and the resulting stress response can cause alterations in the circulating levels of cortisol. These related increases in proteolysis are partly the result of increased circulating levels of catabolic hormones such as cortisol. The resulting levels are high enough to cause the inhibition of protein synthesis and decrease muscle hypertrophy. This is one possible explanation for the mechanisms associated with protein regulation but, it is also important that one considers the interaction between both catabolic (cortisol) and anabolic (testosterone) factors. The combination of the hormonal response to training will not cause immediate protein degradation, rather it is the delicate balance controlling the homeostasis of the body, and in turn the interaction between the production, secretion, metabolic clearance rate of these two opposing hormones that determine muscle responses to exercise (Vailas et al., 1991; Kuppasalmi and Adlercrutz, 1985).

It is well established that muscular activity can influence the size of skeletal muscle, as well as its fundamental biochemical and physiologic properties (Tawa and Goldberg, 1986). Some types of exercise are known to cause compensatory growth in muscle tissue even in the absence of hormonal influences of testosterone, growth hormone, thyroid hormone, and insulin. Thus, it is apparent

that muscular activity is an important trophic factor that can influence muscle size even in the absence of an endocrine response (Tawa and Goldberg, 1986). Tawa and Goldberg (1986) have reported that glycolytic muscle fibers are more sensitive to the catabolic effects of cortisol, than are oxidative fibers. This finding could have important implications in explaining the observed response of muscle and protein synthesis to both prolonged endurance type activities and to short duration exercise, as well as to strength training.

General Response of Cortisol to Exercise

In early studies investigating the effects of exercise on circulating levels of cortisol, changes in the levels of circulating lymphocytes were utilized to reflect fluctuations in adrenal cortex function (Kuoppasalmi and Adlercreutz, 1985). The above response of lymphocytes to altered concentrations of glucocorticoids has important implications in determining the relationship and interaction between the immune and endocrine systems, and their responses to exercise. It is commonly held that the level of circulating cortisol can be determined by analyzing either blood serum or urine, utilizing either single sample or multi-sample methods. The multi-sample urine method ensures that the measurement of cortisol is reflective of the true circulating level verses a single measurement by the blood serum method. The change detected in cortisol levels in response to exercise is directly related to the intensity and duration of activity. Brandenberger et al., (1975) have shown that plasma cortisol will rise independent of the intensity of the workload (low vs. high), as long as the duration of the activity is sufficient.

Brandenberger (1985) states that the majority of studies which have investigated the cortisol response to exercise give conflicting results. Levels of cortisol have been found to remain unchanged, increased, or decreased, depending on confounding variables including the fitness of the subjects, the intensity, or duration of the work loads employed, and the measurement of cortisol (single sample vs multi-sample or blood serum vs a 24 hour urine sample).

Plasma cortisol levels have been found to remain steady during short-term, low to moderate exercise. On the other hand, moderate to heavy exercise consistently causes a rise in plasma cortisol levels. Research conducted by Davis and Few (1973) indicated that a rise in plasma cortisol occurred when the subject reached 60% $\dot{V}O_{2\ Max}$. This was considered to be the critical threshold point. However, intensity of exercise was found to be only one of the contributing factors. Bonen (1976) reported similar results to confirm that cortisol levels correlate positively with the percentage of $\dot{V}O_{2\ Max}$, but additionally found that the duration of the exercise was a contributing factor. It was established that a combination of the above factors resulted in elevated circulating levels of cortisol. It has not been fully determined where the lower limit of the cortisol threshold occurs. The cortisol response to short term exercise is variable because there was a low correlation between the duration and intensity of exercise with the resulting circulating cortisol levels (Bonen, 1976; Kuppasalmi and Aldercreutz, 1985). High levels of cortisol do not appear to be related to exhaustive exercise bouts (Kuoppasalmi and Adlercreutz, 1985).

Comparison of cortisol levels associated with both intense 45 minute and moderate 90 minute exercise bouts showed that the cortisol response was more dependent upon the intensity than the duration of the bout (Kuoppasalmi and Aldercrutz, 1985). Subsequent investigations have illustrated that the metabolism of cortisol is dependent primarily upon the type of exercise itself. If the work bout is at a sufficient intensity, there is an increased rate of uptake of cortisol by peripheral tissue, but the secretion of cortisol reflects concentration levels versus the rate of removal (Kuoppasalmi and Adlercreutz, 1985). Few and Thompson (1980) further confirm this interpretation by demonstrating that continuous running for long distances (100 km) increases the rate of cortisol secretion in fit subjects, but does not alter the metabolism of cortisol. The suppression of

glucocorticoids following high intensity exhaustive exercise functions as a general defense mechanism to prevent a severe reaction and fatal depletion of the resources of the organism (Brandenberger, 1985; Kraemer, 1993; Clarkson and Trembly, 1988).

Other factors influencing the cortisol response to exercise include the fitness and past training of the subject. Conflicting results have been presented in the literature to indicate that fitness may have a positive or neutral effect. In fact, little evidence has been established to outline the precise mechanisms underlying the associated adaptations to training. Lower concentrations have been attributed to a reduction in physiological stress following training. In this respect, variations in cortisol responses can be attributed to conditions of the training environment and to subject perception. Thus, it has been suggested that both the relative contributions of physiological and psychological components of stress during training contribute to the resulting cortisol response (Brandenberger, 1985).

Effects of Strength and Endurance Training on Cortisol

Alen et al. (1988) report that concentrations of serum cortisol, CBG (cortisol binding gobulin), and the cortisol:CBG ratio decreased during a 24 week progressive strength training period. Decreases in cortisol parallelled increased muscular strength. This may indicate a state of decreased catabolic hormonal activity (Alen et al., 1988). Accordingly, the testosterone:cortisol ratio and the free testosterone:cortisol ratio increased reflecting an anabolic state. The above reflects the influence which the balance between anabolic and catabolic hormonal environments can have on muscle protein synthesis. Changes in the concentrations of serum androgens and cortisol are a result of prolonged strength training and characteristically correspond to changes in muscular strength.

The performance of heavy resistance exercise induces acute increases in cortisol in females (Kraemer, 1993). Kraemer (1993) reported that the cortisol response is dependent upon the training protocol employed. Changes in load and rest allowed between sets and exercises is a primary factor contributing to alterations in concentrations of cortisol. Hakkinen et al. (1990) found no changes in serum cortisol levels during a 16 week power training program.

The above agrees with findings reported with endurance trained female athletes (Ronkainen et al, 1986). Hakkinen et al (1990) further states that training in general (strength or endurance) does not appear to have any significant effect on cortisol levels. Conversely, Roberts et al. (1993) reported that cortisol levels were significantly elevated following overtraining. Resting cortisol levels returned to normal following 3 months and did not differ significantly from control subject levels. Additionally, Luger et al (1988) has also reported elevated evening basal ACTH and cortisol levels in resting male long distance runners. These findings are similar to those found in female runners.

Gender Differences

Kanaley et al. (1992) examined and compared the cortisol response of 8 eumenorrheic and 6 amenorrheic athletes throughout 90 minutes of prolonged exercise during three different phases (early follicular, late follicular, and mid-luteal) of the menstrual cycle. Amenorrheic athletes had a significantly different pattern of cortisol response during exercise than the eumenorrheic athletes. A larger cortisol increase was detected in the ammenorrheic athletes versus the eumenorrheic athletes. This finding was largely attributed to disturbance in cortisol secretion in response to the interruption or cessation of the normal menstrual cycle. Kanelay et al (1992) cautioned that alterations in clearance, storage, and feedback mechanisms must also be taken into consideration.

Sustained elevations of cortisol levels in amenorrheic athletes may affect and inhibit both immunologic and inflammatory responses. Long term hypercortisolism is associated with immunosuppression and alterations in calcium and bone metabolism (Kanaley et al., 1992). Kanaley et al. (1992) demonstrated that eumenhorrheic female athletes had a cortisol response to exercise regardless of the phase of their current menstrual cycle. The pattern of cortisol response to exercise is characterized by a small increase followed by a subsequent decrease which lasts the remainder of the exercise bout.

Male athletes also elicit a cortisol response to exercise. Conflicting theories exist as to when the cortisol response occurs. Davis and Few (1973), which state the cortisol response is elicited when untrained male subjects exercise at a minimum intensity of 60% of $\dot{V}O_{2\ max}$. However, Kanaley et al. (1992) suggest that the critical level of exercise intensity is near the individuals anaerobic threshold.

Males and females both elicit a cortisol response to exercise. However, Kanaley et al. (1992) have shown that in females, resting levels of cortisol and the response of cortisol to exercise, are independent of the menstrual phase. This finding is concurrent with those of Ronkanin et al. (1986) who reported that basal cortisol levels do not change with different phases of the menstrual cycle. Thus, the menstrual phase does not influence the cortisol response to exercise (Kanaley et al, 1992).

General Overview of the Human Immune System

The human immune system is a highly complex yet precisely ordered array of cells, hormones, and soluble immunomodulators that inhabit the bone marrow, lymphoid tissues and peripheral circulation. The complexity and diversity of the immune system, as well as its capability to interact with various other physiological systems of the body make it difficult to outline the specific roles and interactions it participates in. Although the immune system affects and is affected by other systems, such as the endocrine system, its primary function is to regulate the body's defense mechanisms against foreign pathogens. It is also involved in the resulting susceptibility, severity, and recovery from infections and illness (Nieman, 1994).

It has been thought that exercise plays an important role in health, and the maintenance of an efficient immune system response. It has been speculated that exercise effectively decreases the occurrence and severity of illness and infection, although the mechanisms are still to be fully explained. In light of the proposed role of exercise and its positive influence on immunity, recently Smith and Weidemann (1990), Neimen (1993), Mackinnion (1992) have speculated that high intensity exercise may act as an immunosuppressor and thus alter the effectiveness of the host defense mechanism.

Currently, research literature exists that reports the effects of exercise on the immune system and its related parameters (Mackinnion, 1992; Neiman, 1993; Neiman, 1989; Haahr et al., 1990; Esperson et al., 1990; Rivier et al., 1994; Smith and Weidman, 1990; Nash, 1994; Valis, 1991). This section will discuss the basic characteristics and mechanisms of response of the immune system and its response. Important rudimentary principles such as the interaction between the endocrine hormones, cytokines, and immune response will be discussed focusing on the involvement of cortisol, testosterone, and tumor necrosis factor-alpha (TNF-α).

The immune system consists of natural (nonspecific) and acquired (specific or adaptive) immune components which act to control and defend against infection. The natural (nonspecific) component of the immune system is referred to as innate immunity. This is the first aspect of the immune system encountered by an invading microorganism. Cells involved with innate immunity can recognize and deal with "nonself" substances without prior exposure. Thus, innate immunity simply distinguishes between self and nonself, and subsequently does not adapt and improve with repeated exposures to the same microorganism (Mackinnon, 1992). The acquired component of the immune system is characterized by specificity to the invading agent and generates memory of prior exposures. Thus, as a result, the acquired component of the immune system response improves with each repeated exposure to an agent (Roitt et al, 1989; Mc Carthy and Dale, 1988; Kimbell, 1986). The acquired component of the immune system is comprised of both antibody and cell mediated immunity (CMI). In both divisions, B and T lymphocytes are primarily found in the lymph nodes and the spleen (McCarthy and Dale, 1988).

Components of the Immune System

A network of host cells which comprise the immune system mediate multiple processes including the recognition of self versus nonself; the elimination of foreign particles and pathogens; neutralizing of toxins; and the killing of tumor cells. One of the most distinguishing features of the immune system is its capacity to recognize and act on specific pathogens via specific immunity. The characteristic of specificity is a property of both T and B lymphocyte cells. Both T and B cells originate in the bone marrow, but mature in the thymus and bone marrow respectively (Kimbell, 1986; Fox, 1990; Arai et al., 1990). There are three basic classes of cells that participate in the immune response that include both T and B cells, as well as macrophages.

Both B and T cells function in specific immunity. The B cells combat bacterial and some viral infections by secreting antibodies into the blood and lymph. Thus, B cells provide humoral immunity. T cells attack host cells that have become infected with viruses or fungi, or transplanted, or cancerous cells. T cells do not secrete antibodies. In order for T cells to be effective, the foreign pathogen must come into close proximity or have actual physical contact with the cell to destroy it. Thus, T cells provide cell mediated immunity (CMI) (Fox et al., 1990).

T cells are also responsible for coordinating the activation of other cells, including B cells. T cells can be subdivided into two types of cells, both having antigen specific receptors on their cell surfaces; Cytotoxic or killer T cells, and T helper cells.

B cells are known as effector cells. Characteristically, these cells are capable of producing and secreting antigen specific immunoglobin molecules that mediate soluble immunity. Additionally, B cells have surface immunoglobins that serve as specific antigen receptors.

Macrophages (refer to diagram on p 146 for origin in Kimball, 1986) are the third class of cells involved in the immune system defense mechanisms. Macrophages are localized in tissues including the spleen, lymph nodes, skin, liver, lungs, and other sites where foreign matter gains access to the body. Some macrophages are actively motile and others such as those in the liver remain fixed in their position. Macrophages, like lymphocytes (T and B cells) are initially derived from the bone marrow and monocytes. These cells are recruited from the blood to serve as a part of the effector system of humoral immunity as well as cell mediated immune responses (Kimball, 1986). Macrophages do not possess any specific antigen-directed capabilities like T and B cells. However, this class of cells is integral in the functioning of the immune system due to the role they play in

the process of antigen presentation to T cells. This process allows T cell recognition of protein antigens and provides both B and T cells with extracelluar signals required for their activation. The interaction between B cells, T cells, and macrophages is very important because it organizes and coordinates the effectiveness of the immune response.

Importance of Cytokines in the Immune Response

Cytokines are important for the interaction between cells in the immune response. Studies by Helle et al, 1988; Mackinnion, 1992; Haahr et al, 1990; Goldberg, 1990; Goodman, 1990, Dinarello, 1989; Chaplin and Hogquist, 1992; Smith and Weidmann, 1990; and Valis, 1991 with natural and recombinant cytokines, have illustrated that most cytokines have multiple biological activities and are multi-dimensional in function on specific genotypes (pleiotropic). Consequently, a cytokine network has been identified that regulates the interactions between lymphoid cells, haematopoietic cells, and the endothelial cell. In this network, a single cytokine can act as both a positive and negative signal depending on its origin, secretion, and target tissue. Through the actions of cytokines, the immune and inflammatory responses can be regulated by the interaction between macrophages and T cells.

The Role of Cytokines

Arai et al. (1990) state that extensive research into the mechanisms of cytokine pathways in vitro suggests that these substances function through a network in vivo. A functional link has been established between lymphocytes and haematopoietic cells. This pathway is formed by multiple cytokines, and results in various biological responses including acute phase reactions. All or part of the above network can be activated via either antigen-specific or non-antigen specific stimuli which are recognized by macrophages and T cells.

Many aspects of the cytokine networks have been established and defined. Accordingly, the various pathways have been outlined and it has been found that the specific cytokine pathways often overlap in both characteristics and function. It has been determined (Harris, 1989; Arai et al, 1990) that most cytokines function at local sites as paracrine or autocrine mediators, and that some act on distant organs and tissues as endocrine mediators. Local effects of cytokines may require a high concentration, whereas systemic effects of cytokines may be induced at relatively low concentrations and successive exposures may be required.

As mentioned above, the acute phase response is associated with tissue injury, and thus may occur with muscle trauma associated with high intensity training and exercise. The acute phase response refers to the response of immune cells to tissue damage, injury, or infection. A large set of proteins known as acute phase reactants (APR) including the C3 component of complement, as well as several other protease inhibitors, are released into the damaged tissue. This response is amplified by glucocorticoid hormones. This response appears to function primarily in limiting tissue damage. The extent and entire functional capabilities of the acute phase response are still to be determined. However, it is known that this response is in part regulated by glucocorticoids which are known to be immunosuppressive (Arai et al., 1990).

It is of interest to highlight the role of cytokines in the inhibition of protein synthesis and proteolysis. Cytokines and other intercellular mediators have the capability to interact with many types of cells and molecules in the body. Much of past research has been focused at the cellular level rather than on the effects on the entire organism. Research now is required to examine the impact on these substances on the homeostasis and physiological parameters of the body (Rothwell & Gimble, 1992). Such changes in the balance of the body's systems can result

from conditions such as infection and inflammatory processes. However, exercise and high intensity physical training also can alter the resting homeostasis of the body and related physiological parameters.

Important advances have been made in the area of physiology with the discovery of cytokines, including Tumor Necrosis Factor-α (TNF-α) and the related intercellular mediators which affect its production, secretion, potency, and action. Cermani and Rowzer (1980) discovered that cells of monocyte/macrophage lineage play a central role in cytokine production and in turn, act to regulate many aspects of both the immune and inflammatory responses. It has been established that these cells play an integral role in the immune response, but lack the specificity and memory capacity characteristic of other immune cells. However, the profound influence elicited by cytokines in the host during the course of inflammation has been shown to be complex (Beutler and Cerami, 1990).

TNF-α

Cytokine substances such as TNF-α, Interleukin 1 (IL-1), and Interleukin 6 (IL-6), have been found to evoke similar actions and participate similarly in inflammation, infection, and the response to injury. TNF-α is one of the most abundant products of activated macrophages, and thus the remainder of the review will highlight its physiological origin, role, actions, and response to injury and inflammation as a result of exercise.

Origin of TNF-α

Tumor necrosis factors (TNF's) are a family of cytokines that are considered to be primary modifiers of the inflammatory and immune reactions of animals and humans produced in response to injury or infection. It is important to outline and understand the general principles underlying the origin and role of the TNF as well as its interaction with other related cytokines which influence the action and role of TNF (Incstar Research Materials, 1993).

Cytokines are a heterogenous group of biologically active protein molecules that regulate cell growth, differentiation and function. They are secreted as soluble mediators, active in very small quantities and may be considered to be a subset of hormones (Meager, 1988). Cytokines are defined as molecules that mediate interactions between cells and are responsible for the communication between immune cells (Mackinnon, 1992). These substances are produced by both lymphocytes and macrophages and encompass a wide variety of families including: the interleukins; tumour necrosis factors; interferons; colony stimulating factors; and transforming growth factors. It is interesting to note that the above families of cytokines are not all individually dependent; rather most cytokines are influenced by other cytokines (ie. INF-$_{\gamma}$, IL-1, IL-2, & IL-6). Of the aforementioned, the relationships between TNF-α, IL-6, and IL-1 and IL-2 will be discussed further.

All of the above cytokines have a common cell of origin and the macrophage plays a integral role in the production of these cytokine molecules. It has been stated that macrophages are the most dynamic producers of intercellular mediators and are normally present in small quantities and numbers (Harris, 1989). However, when the inflammation process has been initiated as a result of injury or disease, the number of macrophages increase due to a migration of these cells from the other areas of the body. As a result, the macrophage enters an activated state, and secretes over 100 substances which have varying effects on surrounding cells. The secretion of theses substances can cause events ranging

from cell growth to cell death. Moreover, individual cytokines may have varying effects on different cell populations. Thus, a cytokine could conceivably exhibit catabolic effects on one specific cell population possibly causing cell death, or conversely exhibit anabolic type actions resulting in a reparative or growth response on a different cell population (Harris, 1989).

Role of TNF

Tumour necrosis factor is a cytokine released by activated B cells, T cells, mast cells and monocytes/macrophages (Rivier et al, 1994) which are structurally related to lymphotoxin. Currently, two forms of the TNF have been identified; TNF-α and TNF-ß. These two forms are distinct in their nature, yet share similar cytotoxic effects on neoplastic cell lines. These two types of TNF are derived and arise from monocytes and lymphocytes respectively. The name of this cytokine indicates that it is capable of causing necrosis in tumours in its purified polypeptide form. The role of this substance in the body is not limited only to acting on tumours. Specifically, TNF-α stimulates fibroblasts, induces bone reabsorption, and inhibits bone formation in vitro. TNF-α is a major inflammatory mediator in the acute phase response of inflammation, thus may play a role in tissue destruction (Rivier et al.,1994) and cachexia (wasting or muscle degradation) (Harris, 1989).

Action of TNF

Contrary to the above described catabolic activities and actions of TNF-α, it is also thought that TNF-α may play an important role in tissue remodelling (Harris, 1989). As previously mentioned, TNF-α as well as TNF-ß stimulate bone reabsorption in addition to participating in the mechanisms of normal tissue repair and remodelling, or healing following inflammatory injury. It has been suggested that TNF-α may also act as a growth factor because it stimulates fibroblasts and induces the production of other cytokines that stimulate cell proliferation and matrix production (Camussi et al, 1991).

It has been reported that TNF-α has a variety of target sites as well as targeted actions. It seems that these substances can act in either a reparative anabolic (Harris, 1989; Camussi et al., 1991), or destructive, catabolic (Rivier et al, 1994; Harris, 1989; Goodman, 1991) manner depending on the specific target tissue. It is important to gain a better understanding of its actions and roles not only in a general sense, but specifically how TNF-α may affect and regulate tissue degradation and repair in relation to exercise.

It has been suggested that TNF-α interacts with various other cytokines and that these interactions result in numerous physiological events. TNF-α has been found to exhibit activities similar to IL-1 which include the induction of the acute phase response, stimulation of monocyte anti-tumour activity, and B and T cell activation (Mackinnon, 1992). Interestingly, TNF-α has not only been identified as having the ability to be very potent alone, but it also participates in a synergist-like action with Interleukin-1. The effects of the coupled action of IL-l and TNF-α on various cells in vitro, as well as systematic effects in vivo, are often biologically indistinguishable. It has been stated (Dinarello,1989) that when the two cytokines are used together in experimental studies, the synergistic effect often exceeds the simple additive effect of each cytokine. This synergism has been demonstrated between these two cytokines in several studies that the author cites (Dinarello, 1989). Additionally, Mackinnion (1992) states that IL-1 and TNF-α may also be involved in tissue degradation and repair following injury, as often occurs during intense activity. Both cytokines stimulate protein catabolism, fibroblast proliferation, collagen synthesis, and are mediators of inflammation.

Dinarello (1989) also proposes that TNF-α and IL-1 participate in a self-augmentation network which acts as an induction mechanism. It appears that human IL-1 and TNF-α are each capable of inducing the production of their own molecules as well as those of one another. The target cells include monocytes, vascular cells (endothelial cells and smooth muscle cells), and B cells. It is

important to realize the capabilities of the TNF-α and IL-1 to produce and reproduce in the self-amplification / augmentation network because of the possibility that this process could play an important role in the degradation of tissues due to the capabilities of these cytokines to sustain the pathogenic process. (Dinarello, 1989).

In addition to the above described relationships, it is of interest to note the influence and relationship of Interleukin-2 with TNF-α. This relationship has importance when considering the role of TNF-α in muscle degradation and repair as a result of prolonged intense physical exercise. In the literature, it has been reported that TNF-α is stimulated and that its release is enhanced by endotoxin (MacKinnon, 1992; Bosenberg et al, 1988). Naturally occurring levels of endotoxin appear to increase following intense prolonged exercise (Bosenberg et al, 1988). If this relationship is significant, it may give an insight into physiological phenomena such as post-exercise muscle soreness or lack of muscle hypertrophy as a result of training (Mackinnion, 1992).

From the above information, it is evident that the roles of cytokines and in particular TNF-α are very diverse, and that their actions have a very wide spectrum. In order to gain a better understanding of these intercellular mediators, research should focus on the conditions in which these substances could play a prominent role.

Cytokines and Exercise

It has been suggested that the physiological consequences of strenuous exercise may be similar but not analogous to those of the acute phase response of inflammation since there are many biological parameters that are increased both after strenuous exercise and in the acute phase reaction (Weight et al, 1991). Cytokines released during the acute phase response such as TNF-α may therefore be of importance in strenuous exercise (Rivier et al, 1994).

As previously stated, TNF-α is capable of eliciting both catabolic and anabolic actions. However, the current literature which investigates the role of cytokines, and TNF-α in particular tends to focus on the catabolic role of TNF in the inhibition of protein synthesis or muscle proteolysis (Esperson et al, 1990; Haahr et al, 1990; Rivier et al, 1994).

Haahr et al.,(1990) measured TNF-α following 60 minutes of submaximal (75% $\dot{V}O_2$ max) exercise on a cycle ergometer. Haahr et al., (1990) expected that TNF would increase 1 hour post-exercise due to the observed increase in monocyte counts. TNF-α did not change following exercise. The lack of change was unexpected and Haahr et al.,(1990) state this finding is unexplainable. Changes in TNF-α were expected to parallel the increases of other monokine-derived cytokines such as IL-1 and IL-6. These findings were not concordant with those of Esperson et al.,(1990). Esperson and associates measured TNF-α levels 2 hours following a 5 km maximal effort run. Results indicate that increases in TNF-α were significant, but returned to nearly normal levels within 24 hours. Although TNF-α levels returned to resting levels, Esperson et al. (1990) suggest that physical exercise can influence parameters of the immune system resulting in both immediate effects and permanent changes in persons who train hard daily. Additionally, the changes in the immune system and cytokine expression in response to exercise are influenced by hormonal factors. The exact triggering mechanism associated with the above has not been identified. However, Esperson et al. (1990) propose that the liberation of cytokines is initiated in response to minor inflammation as a result of microscopic muscle fiber ruptures associated with intense physical activity. In agreement with the findings of Esperson et al. (1990), Smith and Weidemann (1990) have demonstrated increases in plasma TNF-α and IL-1 concentrations with exercise. Levels of TNF-α and IL-1 were significantly higher 3 - 6 hours following moderate intensity running. Smith and Weidemann (1990) state that large increases in monokine concentrations may be detrimental and affect hypothalamic \ pituitary factors which induce ACTH

release. Sustained release of ACTH may contribute to a decreased immune response which is characteristic of athletes training at very high intensities. Smith and Weidemann (1990) speculate that this may be a primary factor influencing the interaction between the immune and endocrine systems, which in turn can affect skeletal muscle homeostasis (Smith and Weidemann, 1990). Rivier et al. (1994) has also investigated the release of cytokines by blood monocytes during strenuous exercise. TNF-α levels were measured before, immediately after, and 20 minutes after strenuous interval-type exercise in a group of young elite endurance athletes and a group of master athletes. Findings indicated that serum TNF-α levels were always undetectable except in one case (15 pg/ml), and levels did not increase after exercise. TNF-α in vitro was slightly but not significantly increased following exercise and slightly but not significantly decrease during post-recovery. Thus, monocytes do not release more TNF-α before, during, or after exercise (Rivier et al, 1994). Additionally, Rivier et al (1994) suggest that the above results may be explained because of the correlation between TNF-α release and intensity of exercise, and the accompanying release of adrenalin. Adrenalin is known to play an important role in the physiological changes observed during exercise (Rivier et al, 1994). Rivier et al., (1994) found that an injection of adrenalin induces the same effects as exercise on the immune system. The effects of adrenalin may explain why the release of TNF-α in not increased during exercise (Rivier et al., 1994).

The above findings of Rivier et al.(1994) are concordant with those of Haahr et al.(1990) who indicated that exercise does not cause any changes in TNF-α release by monocytes. However, these findings differ from those of Esperson et al. (1990) and Smith and Weidemann (1990). The above highlights the changes of monocyte derived cytokines in response to acute exercise. However, the literature lacks studies investigating TNF-α and other monocyte derived cytokines in relation to chronic, long term training.

Exercise, Endocrine, and Immune System Interactions

Several investigators including Esperson et al. (1990); Harbour-McMenamin and Blalock (1989); Vailas et al. (1991); Goodman (1993); Gilbert and Payan (1991); and Wick et al (1993) have suggested that both the immune and endocrine systems do not function in an independent manner. Rather, each systems response, regulation, and function is dependent upon the other, as well as upon the surrounding environment. This new line of thinking is contrary to past beliefs that the endocrine system and the immune system were autonomous networks functioning to maintain a balance between the environment and the host. The endocrine system was believed to respond to external stimuli such as stress and the immune system to the exposure of bacteria, trauma, and viruses (Gilbert and Payan, 1991). In the past 20 - 30 years, studies completed in the area provide sufficient evidence to demonstrate that the endocrine system provides some level of regulation of immune function indirectly via centrally controlled hormones, or directly through the release of neurotransmitters (Harbour-McMenamin and Blalock, 1989; Gilbert and Payan, 1991; Blalock, 1990). The possibility of a direct line of communication between the endocrine and immune systems is credible (Wicks et al., 1993; Gilbert and Payan, 1991) due to the majority of the lymphoid tissues being innervated (Harbour-McMenamin and Blalock, 1989). Hence, the relationship lies in both endocrine and lymphoid tissues being stimulated neurologically. Additionally, Harbour-McMenamin and Blalock, (1989) and Gilbert and Payan (1991) state that the line of communication between the endocrine and immune systems appears to be bi-directional. Thus, the function of each independent system may result in alterations in the functions of the other.

Accordingly, the importance of investigating the interaction between the endocrine and immune systems in response to external stimuli, such as exercise is evident (Esperson et al., 1990; Vailas et al., 1991). Exercise is known to result in alterations in the homeostatic balance of the body which in turn stimulate

adaptation. However, if changes in the homeostatic balance are very extreme, the body sometimes fails to fully adapt and recover (Vailas et al., 1991).

It is well accepted that intense training sessions produce micro-trauma to muscle fibers and minor inflammation (Esperson et al, 1990). However, under normal conditions, recuperation and adaptation of the muscle occurs within 12 to 48 hours. If the muscle fails to recuperate and regeneration is slowed, normal protein synthesis may be inhibited (Vailas et al., 1991). The mechanisms underlying this condition are not fully explained, but research presented by Barron et al. (1989); Vailas et al., (1991); and Shinkai et al. (1993) suggest the lack of recovery could be a result of altered interactions between the immune and endocrine systems, thereby affecting musculoskeletal homeostasis. Further, it has been hypothesized by Barron et al. (1989) that overtrained athletes maintain a higher level of cortisol as well as a higher exercise-induced level of plasma catecholamines. Increases in both parameters are known to cause immune suppression as a result of alterations and increases in leucocytosis (Vailas et al., 1991).

Changes of the endocrine regulated immune responses affiliated with intense training are phasic and correspond to training volumes and recovery. Vailas et al. (1991) state that strenuous training alters both cell mediated immunity and antibody mediated immunity. Consequently, during periods of intense training when the athlete is unable to fully recover, susceptibility to low grade infections increase due to the sustained elevation of basel plasma cortisol level (Vailas et al., 1991). Of even greater interest, are the effects that the altered homeostasis has on tissue maintenance and growth. Changes in both the immune and endocrine systems are known to control the process of tissue degradation and remodelling (Goodman, 1993; Goodman, 1991; Vailas et al., 1991). The above has been described as a steady-state equilibrium between tissue catabolism and anabolism (Vailas et al., 1991). Further, Vailas et al. (1991) state the physiological

manifestations associated with long term intense training result in changes of the morphologic and biochemical properties of musculoskeletal tissue. Increases in tissue catabolism is thought to be a continual process manifested over time as a result of changes in the levels of cortisol, catecholamines, testosterone, and cytokines (Vailas et al., 1991). The net effect of the above process is to produce alterations in the basal metabolism of musculoskeletal tissue. Gradually, there is a shift from a balanced homeostatic state to a more predominantly catabolic state, with a progressive increase in basal proteolytic activity in skeletal muscle (Vailas, 1991).

Goodman (1993) further supports Vailas et al.,(1991) by stating metabolic changes in muscle tissue may be mediated in part by alterations in the effectiveness or in the concentrations of insulin, glucagon, catecholamines, and glucocorticoids. Further, Goodman (1993) argues that the above may be mediated in part, or initiated by changes in circulating polypeptides released by stimulated macrophages or lymphocytes. This group of polypeptides consists of cytokines including TNF-α, IL-1, and IL-6. The specific role played by each of these intercellular mediators is still not fully understood. However, it is believed that they play a significant role in tissue proteolysis (Goodman 1993; Goodman, 1991; Vailas et al, 1991).

Much of the research investigating the role of cytokines and glucocorticoids in tissue degradation have utilized animal models concentrating on pathological processes including sepsis, high grade infections, and inflammatory disorders (Goodman, 1993). This research has important implications elucidating the interaction between the immune and endocrine systems in exercise-related tissue alterations. Similar to infection and sepsis, exercise also causes an increased expression of endotoxin (Mackinnon, 1992; Bosenberg et al., 1988). Goodman et al. (1993) have previously demonstrated that during sepsis or after the experimental administration of bacterial endotoxin there is a large increase in

muscle protein breakdown. This response may be mediated by glucocorticoids or by various cytokines (Goodman, 1993). Goodman (1993) states the results from current research in his laboratory suggest that glucocorticoids, as well as TNF-α and IL-6 play roles in the enhanced muscle proteolysis. Harris (1989) and Beulter and Cerami (1990) also agree that IL-1 plays a role in increased muscle proteolysis. As mentioned previously, TNF-α and IL-1 have been described as participating in a self-augmentation network (Harris, 1989). However, contrary to this finding, early studies (Klien et al., 1991; Martin, 1981) with TNF-α and IL-1 have failed to demonstrate that these cytokines can augment muscle proteolysis. Rather, more recent studies (Klien et al, 1992; Samarel and Engelmann, 1991) have demonstrated that these cytokines are more effective as mediators, rather than effectors.

Serum glucocorticoids, TNF-α, IL-1, and IL-6 have been found to be elevated in endotoxin treated rats (Goodman, 1993) and each of these soluble mediators have been shown to be capable of augmenting muscle proteolysis (Goodman, 1993). However, it has been suggested that each of the above play a distinct role and are potent at disparate times. Goodman (1993) found serum TNF-α to be elevated early, while the rise in serum IL-6 and glucocorticoids followed. This may suggest that TNF orchestrates the muscle proteolytic response, and that IL-6 and the glucocorticoids are the causative agents. This scheme seems plausible since TNF-α can induce the production of IL-6 (Goodman, 1993). Additionally, Goodman (1993) states the effects of TNF-α and of IL-6 on muscle proteolysis are mediated indirectly and induce other mediators that trigger muscle proteolysis.

The above demonstrates that the role and interaction of cytokines, and in particular TNF-α are not fully clarified. However, evidence presented by Goodman (1993; 1991) eludes to cytokines and glucocorticoids as playing important roles in proteolysis and protein turnover of skeletal muscle tissue.

Several implications regarding the biological interactions displayed by these cytokines make it difficult to distinguish the exact physiological processes taking place, particularly when exercise becomes a factor. Smith and Weidemann (1990) have attempted to determine the effects of different types of physical exercise affecting the endocrine and immune systems, and in turn the homeostasis of musculoskeletal tissue. Smith and Weidemann (1990) propose the type (aerobic versus anaerobic) and intensity of exercise play a role in the response and the interaction between the endocrine and immune systems, and in turn skeletal muscle homeostasis. Research conducted by Smith and Weidemann (1990) indicates that aerobic and anaerobic modes of exercise result in disparate impacts on both the immune and endocrine systems (Smith and Weidemann, 1990). Additionally, Smith and Weidemann (1990) suggest low intensity exercise may act to boost or enhance the immune system response, while the opposite is true with moderate to high intensity exercise. Thus, the duration and intensity of exercise determines the magnitude of response altering circulating levels of catecholamines, cortisol, and the immune response. These actions may be exerted by means of a humoral mechanism and result in a behavioral effect on cellular immunity. Smith and Weidemann (1990) report that the depression of some immune cell functions in response to traumatic stress shows similarity to the changes resulting from intensive training.

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